

# Curative resection of combined neuroendocrine carcinoma and adenocarcinoma of the gallbladder

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## ABSTRACT

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Neuroendocrine carcinoma of the gallbladder has very rarely been reported as it accounts for only 0.5% of all neuroendocrine tumors. It has a very aggressive biological behavior. These tumors are usually diagnosed at an advanced stage and surgical management is therefore not an option. We performed a hepatopancreaticoduodenectomy along with adjuvant chemotherapy in a 48-year-old patient with a neuroendocrine carcinoma of the gallbladder. The patient has been followed up at the outpatient clinic for 18 months without there having been any recurrence. Patients with a locally invasive neuroendocrine carcinoma in the gallbladder may benefit from aggressive surgical treatment followed by adjuvant chemotherapy. The primary management in high-grade metastatic tumors is, however, mainly medical.

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## Introduction

The incidence of neuroendocrine tumors (NETs) has been increasing every year by 6%<sup>1</sup>. NETs mostly occur in the gastrointestinal tract (66%) or the bronchopulmonary system (31%), but they may also occur in the ovary, testis, hepatobiliary system and pancreas<sup>1</sup>. NETs in the gallbladder account for 0.5% of all NETs and 2% of all gallbladder cancers<sup>2</sup>. Small-cell neuroendocrine carcinoma is a poorly differentiated neuroendocrine carcinoma that has rarely been reported. These tumors may contain well-differentiated neoplastic glands like adenocarcinoma or squamous cell carcinoma (Table 1)<sup>3,4</sup>. Generally, the biological behavior of neuroendocrine carcinoma is more aggressive than that of adenocarcinoma<sup>5</sup>. When neuroendocrine carcinoma is accompanied by adenocarcinoma, the prognosis is determined by the progression of the neuroendocrine carcinoma<sup>5</sup>. Neuroendocrine carcinomas are usually diagnosed at an advanced stage and surgical management is therefore not a therapeutic option. Although these tumors can be treated when they are detected at an early stage, the prognosis is very poor, with a 5-year survival rate of less than 10%<sup>4,6</sup>. We report a rare case of neuroendocrine carcinoma combined with adenocarcinoma in the gallbladder that was treated by curative resection (hepatopancreaticoduodenectomy and right hemicolectomy).

## Case report

A 48-year-old woman complained of a palpable mass and discomfort in the right upper quadrant of the abdomen. On physical examination, a firm, fixed mass was found in the right upper quadrant of the abdomen, but there was no tenderness or rebound tenderness. The levels of hepatic and biliary enzymes were normal except for a lactate dehydrogenase (LDH) level of 692 IU/L (normal range: 218-472 IU/L). The levels of the tumor markers carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9) and alpha-fetoprotein (AFP) were also normal.

Upper abdominal ultrasound examination revealed a 7.5-cm gallbladder mass with direct invasion of the liver parenchyma. Abdominal computed tomography (CT) and

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**Table 1 - WHO classification of neuroendocrine tumors of the gastroenteropancreatic system**

1a	Well-differentiated neuroendocrine tumor (WHO 1)
1b	Well-differentiated neuroendocrine carcinoma (WHO 2)
2	Poorly differentiated neuroendocrine carcinoma (WHO 3)

magnetic resonance imaging demonstrated a 7.5-cm mass lesion that was attached to the colon and duodenum through the pericholecystic fat and had also invaded the liver parenchyma at a depth of over 2 cm (Fig-

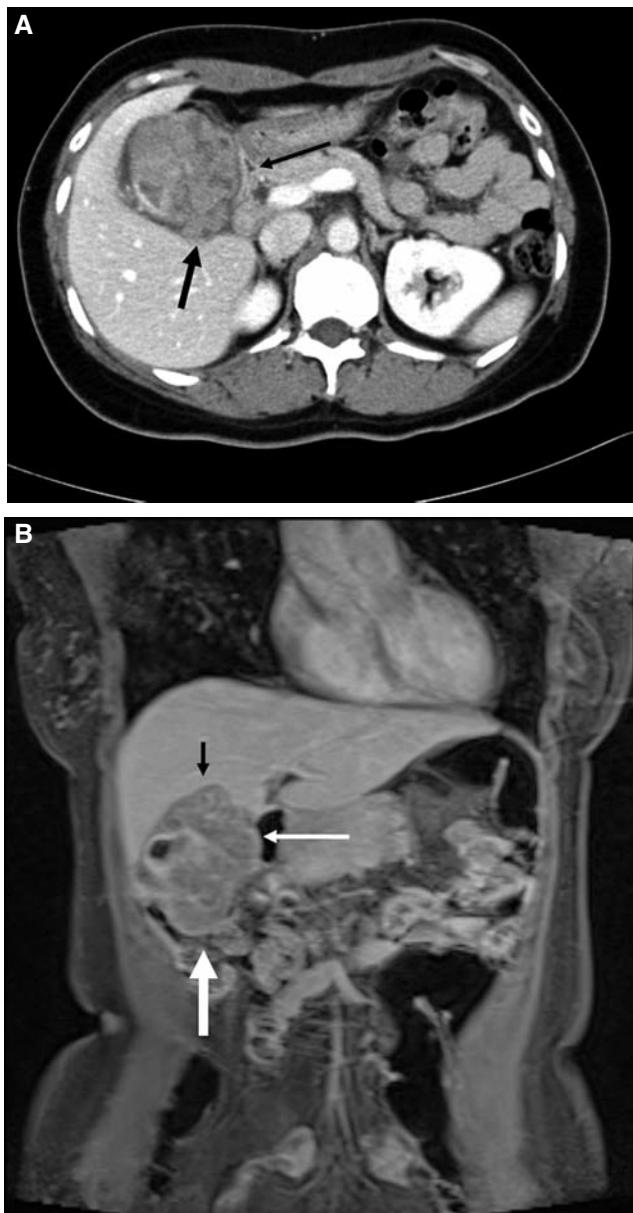


Figure 1 - A) A large gallbladder mass has invaded the duodenum (thin arrow) and liver (thick arrow), as seen on the contrast-enhanced CT scan. B) The T1-weighted MR image shows a large gallbladder mass that has invaded the liver (black arrow), duodenum (thin white arrow) and colon (thick white arrow).

ure 1). An anomalous union of the pancreaticobiliary duct was demonstrated on magnetic resonance cholangiopancreatography (Figure 2). Gastroduodenoscopy and colonoscopy showed no abnormal findings of the mucosa. A hypermetabolic lesion ( $SUV_{max}$  11.0) in the entire gallbladder was shown on  $^{18}F$ -FDG PET/CT, which was performed to check for distant metastasis. No distant metastasis was detected.

After a needle biopsy, small-cell neuroendocrine carcinoma was diagnosed because small-cell cytological features were seen on microscopy. The immunohistochemical staining result was CD56(+)/NSE(-)/chromogranin A(-)/CK7(-)/CK20(-).

We performed a hepatopancreaticoduodenectomy (S4b+S5 segmentectomy) and right hemicolectomy simultaneously. We also performed dissection of the lymph nodes around the hepatoduodenal ligaments and the celiac trunk. Histopathology showed a collision tumor that consisted of small-cell neuroendocrine carcinoma and moderately differentiated adenocarcinoma with a transitional zone (Figure 3). The size of the tumor was 9.5 × 9.3 × 6.5 cm. Ninety percent of the tumor was a neuroendocrine carcinoma, which showed a CD56(+)/synaptophysin(-)/chromogranin A(-) staining pattern, and the other 10% of the tumor was an adenocarcinoma that showed a CK7(-)/CK19(+)/CK20(+)/CDX2(+) staining pattern on immunohistochemistry. Necrosis was observed in 10% of the tumor. The component with direct invasion of the liver parenchyma and duodenum consisted of small-cell neuroendocrine carcinoma (T3N0M0, stage IIIA). Intestinal metaplasia was shown in the rem-



Figure 2 - T2-weighted magnetic resonance cholangiography shows an anomalous pancreaticobiliary ductal union (arrow).

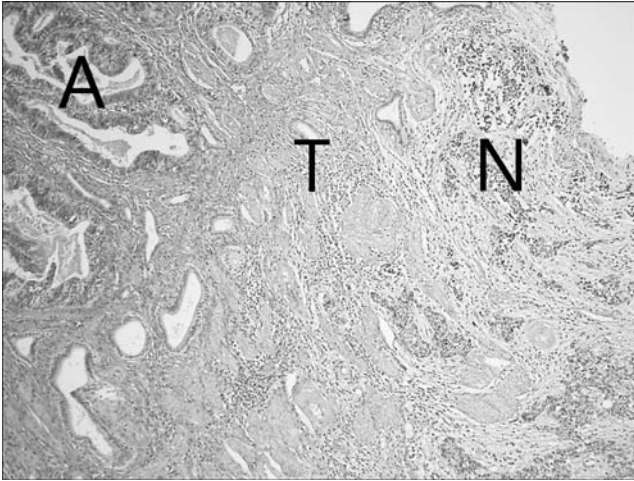


Figure 3 - The gallbladder collision tumor consisted of adenocarcinoma cells and small-cell neuroendocrine carcinoma cells with a transitional zone. (H-E stain,  $\times 100$ ) (A: adenocarcinoma cells, T: transitional zone, N: small-cell neuroendocrine carcinoma cells)

nant gallbladder tissue. One metastatic lymph node of the 39 resected lymph nodes contained adenocarcinoma (T2N1M0, stage IIIB). Lymphovascular invasion was shown in the adenocarcinoma component. The tumor-free margin at the liver was 1.0 cm. The duodenum was directly invaded by a  $1.2 \times 0.5$  cm tumor lesion into the serosal layer, but there was no direct invasion into the resected right colon.

The patient was discharged from the hospital on the 20th postoperative day without any complications. She subsequently underwent 6 cycles of adjuvant chemotherapy composed of 5-FU ( $1000 \text{ mg/m}^2$ ) and cisplatin ( $60 \text{ mg/m}^2$ ). She has been followed up at the outpatient clinic without a recurrence for 18 months. An abdominal CT scan was performed every 3 months during the first 6 months and every 6 months thereafter.

## Discussion

Neuroendocrine cells do not normally exist in the mucosa of the gallbladder, so neuroendocrine tumors should ideally not occur in this organ. Three controversial theories have been proposed for the histogenesis of combined neuroendocrine carcinoma and adenocarcinoma. First, the 2 components may originate simultaneously from 2 different precursor cells. Second, one component may produce the other. Third, a totipotent progenitor cell may produce both components<sup>7</sup>. Our patient had an abnormal hepatobiliary junction and intestinal metaplasia. We suggest that the neuroendocrine tumor could have occurred due to the neuroendocrine cells or multipotent stem cells that arose from the intestinal metaplasia at the gallbladder mucosa because an abnormal hepatobiliary junction can induce chronic inflammation<sup>3</sup>. The WHO definition of small-cell neuroendocrine carcinoma is more than 10 mitoses/ $\text{mm}^2$ , small-cell cytological features, and strong positivity for neuroendocrine markers (such as chromogranin A and synaptophysin)<sup>3</sup>. In this case, the cytological features were typical of small-cell neuroendocrine carcinoma and there were 12 mitoses/ $\text{mm}^2$ . Although the results of staining for chromogranin A and synaptophysin were negative, another neuroendocrine marker (CD56) showed positivity.

Small-cell neuroendocrine carcinoma is characterized by aggressive behavior and early local or distant spread<sup>8,9</sup>. Small-cell neuroendocrine carcinoma of the gallbladder may be unresectable by the time of its detection because of the large volume and the invasion of adjacent organs such as the liver, duodenum, and pancreas. These tumors do not usually respond to radiotherapy or chemotherapy; the median survival is only 4 months and the 5-year survival rate 8%<sup>3,10</sup>. Thirty-four cases of combined neuroendocrine carcinoma and adenocarcinoma of the gallbladder were reported up to 2002 in Japan. Nearly all reported cases were diagnosed at an advanced stage and almost all patients died within 1 year<sup>11</sup>. Our patient was also diagnosed at an advanced stage, but she had no hepatic vascular invasion or distant organ metastasis. Because we could expect a good survival in this case, we tried an aggressive surgical approach. Aggressive multimodality treatments such as surgery with chemotherapy are the only way to increase the survival rate<sup>3,12</sup>. Although performing a hepatopancreaticoduodenectomy in a patient with advanced gallbladder cancer is generally debatable, it can be performed when the cancer invades the duodenum, pancreas or lymph nodes around the pancreas directly<sup>13</sup>. Patients should be carefully selected for hepatopancreaticoduodenectomy because the mortality and morbidity of the procedure are very high at 5-35% and 30-100%, respectively<sup>13</sup>.

We opted for this aggressive approach because the patient was a young woman without any other diseases. Moreover, the preoperative imaging studies showed no distant metastasis and no extensive lymph node metastasis and we thought the locally invasive gallbladder carcinoma could be treated with R0 resection. The extent of lymph node dissection in gallbladder carcinoma is still a matter of debate, but in South Korea it usually includes the lymph nodes around the hepatoduodenal ligaments and those behind the head of the pancreas and hepatic artery. The lymph nodes around the superior mesenteric vessel and aorta were also dissected in this case. One lymph node (1/39) around the hepatoduodenal ligament was confirmed to contain metastasis. Although the relationship between the extent of lymph node dissection and prognosis has not yet been ascertained, aggressive lymph node dissection should be performed because accurate lymph node staging can be helpful in the choice of the appropriate adjuvant treatment.

The prognosis of advanced gallbladder adenocarcinomas (over stage III) is also very poor, with a 5-year survival rate of less than 10%<sup>14</sup>. In this case the adenocarcinoma component had metastasized to 1 lymph node and there was also lymphovascular invasion. We believed surgical resection was sufficient to treat the neuroendocrine carcinoma component because it showed only local invasion. Although neuroendocrine carcinomas of the gallbladder behave more aggressively, the adenocarcinoma component showed a more advanced stage in our patient and so there could be systemic metastasis. The patient was therefore given chemotherapy for adenocarcinoma of the gallbladder.

### Conclusion

For young, healthy patients with neuroendocrine carcinomas of the gallbladder, aggressive surgical treatment followed by adjuvant chemotherapy should increase the survival rate despite the cancer's high mortality and morbidity. Further studies are needed to confirm the benefit of aggressive treatment for patients with neuroendocrine carcinoma of the gallbladder.

### References

- Gustafsson BI, Kidd M, Modlin IM: Neuroendocrine tumors of the diffuse endocrine system. *Curr Opin Oncol*, 20: 1-12, 2008.
- Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB: One hundred years after "Carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*, 26: 3063-3072, 2008.
- Eltawil KM, Gustafsson BI, Kidd M, Modlin IM: Neuroendocrine tumors of the gallbladder: an evaluation and re-assessment of management strategy. *J Clin Gastroenterol*, 44: 687-695, 2010.
- Moskal TL, Zhang PJ, Nava HR: Small cell carcinoma of gallbladder. *J Surg Oncol*, 70: 54-59, 1999.
- Shimizu T, Tajiri T, Akimaru K, Arima Y, Yoshida H, Yokomuro S, Mamada Y, Taniai N, Mizuguchi Y, Kawahigashi Y, Naito Z: Combined neuroendocrine cell carcinoma and adenocarcinoma of the gallbladder: report of a case. *J Nihon Med Sch*, 73: 101-105, 2006.
- Soga J: Primary endocrinomas (carcinoids and variant neoplasms) of the gallbladder. A statistical evaluation of 138 reported cases. *J Exp Clin Cancer Res*, 22: 5-15, 2003.
- Eriguchi N, Aoyagi S, Noritomi T, Imamura M, Sato S, Fujiki K, Furukawa S, Shirozu K, Hayashi I: Adeno-endocrine cell carcinoma of the gallbladder. *J Hepatobiliary Pancreat Surg*, 7: 97-101, 2000.
- Duan HJ, Ishigame H, Ishii Z, Itoh N, Shigematsu H: Small cell carcinoma of gallbladder combined with adenocarcinoma. *Acta Pathol Jpn*, 41: 841-846, 1991.
- Modlin IM, Lye KD, Kidd M: A 5-decade analysis of 13,715 carcinoid tumors. *Cancer*, 97: 934-959, 2003.
- Albores-Saavedra J, Batich K, Hossain S, Henson DE, Schwartz AM: Carcinoid tumors and small-cell carcinomas of the gallbladder and extrahepatic bile ducts: a comparative study based on 221 cases from the Surveillance, Epidemiology, and End Results Program. *Ann Diagn Pathol*, 13: 378-383, 2009.
- Tsuchiya A, Endo Y, Yazawa T, Saito A, Inoue N: Adenoendocrine cell carcinoma of the gallbladder: report of a case. *Surg Today*, 36: 849-852, 2006.
- Nishime C, Ohnishi Y, Suemizu H, Tamaoki N, Kusumi T, Sato F, Yamazaki H, Nakamura M, Ueyama Y, Kijima H: In vivo chemotherapeutic profile of human gallbladder small cell carcinoma. *Biomedical Research*, 29: 251-256, 2008.
- Park SJ: Extent of surgical resection in gallbladder cancer. *Korean J HBP Surg*, 13: 84-88, 2009.
- Gallbladder. In: *AJCC Cancer Staging Manual* (7th ed), Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (Eds), pp 211-217, Springer, New York, 2009.