Mixed Adenoneuroendocrine Carcinoma Arising in a Papillary Adenoma of Gallbladder

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Abstract:
Introduction: Neuroendocrine carcinoma and mixed adenoneuroendocrine carcinoma (MANEC) in the gallbladder are rare. Here, we reported an unusual case of a mixed high-grade neuroendocrine carcinoma and adenocarcinoma, arising in a papillary adenoma with high-grade dysplasia.

Presentation of case: The patient, a 73 year-old woman, had a cholecystectomy for chronic calculous cholecystitis, in which a mixed high-grade neuroendocrine carcinoma and adenocarcinoma arising in a papillary adenoma with high-grade dysplasia was incidentally noted. The carcinoma invaded into lamina propria, without any evidence of invasion into muscularis layer or perimuscular soft tissue, hence was pathologically staged as T1. The patient was treated with chemoradiation after cholecystectomy. Despite the unusually low tumor stage at presentation of this rare tumor, there were four recurrences / metastases involving abdominal wall, an unusual site for this tumor, which were treated with surgery and / or chemotherapy. The patient is alive with metastatic disease at 45 months after initial cholecystectomy.

Conclusion: We detail the unusual presentation of a mixed high-grade neuroendocrine carcinoma and adenocarcinoma arising in a papillary adenoma with high-grade dysplasia, which sheds some light on the clinical course of this rare tumor.

Keywords: MANEC; neuroendocrine carcinoma; adenoneuroendocrine carcinoma; gallbladder; papillary adenoma

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Introduction

Neuroendocrine carcinomas represent 4% of all malignant neoplasms of the gallbladder and mixed adenocarcinoma and neuroendocrine carcinomas of the gallbladder are rarer [1, 2]. In the World Health Organization (WHO) 2010 classification of gallbladder tumors, mixed adenoneuroendocrine carcinomas (MANECs) are composite neoplasms in which areas of adenocarcinoma or squamous cell carcinoma intermingle with areas of neuroendocrine tumor or neuroendocrine carcinoma, each comprising at least 30% of the neoplasm [3]. There are isolated case reports of such tumors, all of which presented as a large mass in the gallbladder [2, 4-8]. To our knowledge, this is the first reported case of a mixed high-grade neuroendocrine carcinoma and adenocarcinoma arising in a papillary adenoma of the gallbladder, which was confined to the lamina propria and staged as pT1, yet displayed an aggressive course.

Case presentation

Our patient was a 73-year old woman with a remote history of breast carcinoma diagnosed 22 years ago, for which she was treated with lumpectomy followed by radiation. Subsequently, there was no recurrence of this disease. She was an occasional smoker till 50 years of age, described as ‘social smoking’ but she would also go long periods without smoking at all, until she finally quit. She underwent an elective laparoscopic cholecystectomy for cholelithiasis at an outside hospital. On gross examination, a 6.0 x 2.8 x 0.7 cm previously opened gallbladder was received with a 2.0 cm green friable calculus as well as a separate 1.5 x 0.6 x 0.6 cm aggregate of green grumous soft tissue, possibly representing a dislodged friable polyp. The gallbladder had a wall thickness of 0.2 cm, and a pink velvety, grossly unremarkable mucosa. There was no mass or ulcerated lesion grossly identified in the gallbladder.

Histologically, the polypoid tissue revealed a biliary type papillary adenoma with focal high-grade dysplasia and conventional invasive moderately differentiated adenocarcinoma, which comprised approximately 30% of the entirely submitted tumor. The rest of the polyp (70%) was composed of solid sheets and cords of small mononuclear cells with high nuclear: cytoplasmic (N: C) ratio, more than 60 mitoses per 10 high power fields and scattered areas of necrosis. Immunohistochemistry on the solid tumor component was positive for synaptophysin (Novocastra, 27G12, 1: 600) and chromogranin A (Chemicon, LK2H10, 1: 4000), but was negative for estrogen receptor (Novacastra, ER 6F11, 1: 35), progesterone receptor (Dako, PgR 1294, 1: 200) and mammaglobin (Biocare Medical, PM 269 AA, H, predilute). Pan-cytokeratin (Dako, Z0622, 1: 100) stain was strongly positive in both components. Sections from the entirely submitted gallbladder revealed chronic cholecystitis, but no evidence of dysplasia or invasive carcinoma. Therefore the diagnosis of a mixed high-grade neuroendocrine carcinoma and adenocarcinoma arising in a papillary adenoma with high-grade dysplasia of gallbladder was rendered. The carcinoma invaded into lamina propria, without any evidence of invasion into muscularis layer or perimuscular soft tissue, hence was pathologically staged as T1. No lymphovascular or perineural invasion was identified. The cystic duct margin was negative for dysplasia or carcinoma.

The patient fully recovered from the cholecystectomy without any complication. The computed tomography (CT) scan performed three weeks after cholecystectomy did not reveal any adenopathy or metastatic disease. She received 25 fractions of external beam radiotherapy for a month with 5-fluorouracil and was thereafter placed on clinical surveillance. Eleven months after the cholecystectomy, a CT scan revealed an enhancing soft tissue nodule on the anterior abdominal wall...
near umbilicus, with subcutaneous and intraperitoneal components. She underwent a wide excision of the umbilical mass, which revealed a mixed high-grade neuroendocrine carcinoma and moderately differentiated adenocarcinoma, consistent with metastasis from primary gallbladder carcinoma. Six months after wide excision of the umbilical mass, she was found to have a 14 mm subcutaneous nodule in the right lower quadrant and underwent ultrasound guided fine needle aspiration (FNA), which revealed metastatic carcinoma, morphologically consistent with the patient’s known gallbladder primary. She subsequently underwent excision of the subcutaneous nodule, which showed a metastatic high-grade neuroendocrine carcinoma. The patient then received 8 cycles of chemotherapy consisting of gemcitabine and oxaliplatin, at doses of 1000 mg / m2 and 100 mg / m2, respectively, given every other week for 4 months, which caused significant peripheral neuropathy. Fifteen months after the completion of chemotherapy, 3 new soft tissue nodules were identified within the anterior abdominal wall muscle with the largest being 3.5 cm by CT scan and were excised, all of which showed mixed high-grade neuroendocrine carcinoma and adenocarcinoma consistent with the gallbladder primary. Four months later, she was found to have a 4 x 3.5 cm mass within the rectouterine pouch as well as a small nodule in the omentum. Due to close proximity of the tumor to the bladder and rectum, surgical resection was considered too risky and she was referred to our institution. Considering palliation and avoidance of medication which would exacerbate her peripheral neuropathy, she was treated with FOLFIRI chemotherapy (irinotecan 180mg / m2, 5-fluorouracil 2400 mg / m2 and leucovorin 400mg / m2 given over 46 hours, for 4 - 6 times over 2 months). She responded modestly, and currently the patient is alive with unresectable metastatic disease in the omentum and cul-de-sac at 45 months after the initial cholecystectomy. She feels relatively well apart from a painful peripheral neuropathy in both her legs secondary to previous oxaliplatin treatment. The only medications she is on is Neurontin 2 tabs p.o. at bedtime for her neuropathy and synthroid, 112 mcg 1 tab p.o. daily.

Discussion

Based on the strict definition of MANEC, at least 30% of the tumor needs to have a malignant neuroendocrine component and an adenocarcinoma component. Therefore, both components are usually readily appreciable on routine H&E staining, with the adenocarcinoma component identified by gland formation, having cytologic features of prominent nucleoli and vesicular nuclei and the neuroendocrine component showing sheets, nests or trabeculae of cells with high nuclear-cytoplasmic ratio and granular chromatin. Immunohistochemically, the characteristic staining pattern is distinct in the two areas of this mixed tumor, which helps establish the diagnosis of this tumor based on the extent of staining with specific neuroendocrine markers. The prognosis of high-grade neuroendocrine carcinoma of the gallbladder is poor and 40 - 50% of the reported cases presented with disseminated disease at the time of diagnosis [3, 9]. Given the rarity of the MANEC of gallbladder, the clinical course of this tumor is not clear. According the WHO, MANECs behave as adenocarcinomas and are clinically more aggressive than neuroendocrine tumors [3]. However, a study of MANECs from the hepatobiliary system, including five gallbladder MANECs, by Harada et al suggested that the neuroendocrine carcinoma component defined the prognosis [10]. Although there is currently no data enumerating survival time in cases of gallbladder MANECs, in a study by la Rosa et al, the 5 year survival of gastrointestinal MANECs was 36% [11]. The follow up of our patient showed an unusual pattern of recurrence/metastasis than those observed in conventional gallbladder carcinomas, in which metastatic disease typically involves the lymph nodes and intraabdominal organs such as
liver and peritoneum [12]. The current treatment strategy for MANEC involves treatment of the more aggressive component of the tumor. In a MANEC containing a well differentiated neuroendocrine component and an adenocarcinoma component, it should be treated as adenocarcinoma. If a MANEC contains a poorly differentiated neuroendocrine component, it should be treated as a poorly differentiated neuroendocrine tumor [11].

According to la Rosa et al, till date, about 60 cases have been reported from the gastrointestinal tract. There is slight male prediliction, with mean age at diagnosis being 65 years (32-87 years). Tumors in the stomach are predominantly described as polypoid, while from the intestines, they are usually large and constricting [11].

Figure 1 A and B: H&E, 10X. Mixed adenoneuroendocrine carcinoma (MANEC) invading lamina propria. No muscle invasion is seen.
Our patient did not have liver or lymph node involvement during the course of her disease, but had multiple recurrences / locoregional metastases involving abdominal wall. Since the gallbladder was received in a previously cut-open state and the polyp was fragmented, we cannot exclude the possibility that the abdominal wall recurrences / metastasis may represent drop recurrence / metastasis from the initial cholecystectomy, which was done laparoscopically without any clinical suspicion and therefore gross inspection or lavage of the peritoneal cavity was not done.

Similar to our case, association of neuroendocrine tumors with gallstones has been reported [13]. However, the histogenesis of neuroendocrine tumors in the gallbladder is uncertain since normal gallbladder mucosa does not contain neuroendocrine cells, except for the gallbladder neck region [14]. It has been postulated that neuroendocrine tumors of gallbladder may arise from gastric or intestinal metaplasia, which contains a neuroendocrine cell component, secondary to chronic inflammation; from progenitor cells with multidirectional differentiation potential [15], or from aberrant differentiation toward neuroendocrine cells of adenocarcinoma [7].

![Figure 2](image_url) Figure 2A: H&E, 4X. Adenocarcinoma component (lower left) and high grade neuroendocrine carcinoma component (upper right). Figure 2B: Chromogranin immunostain, 4X. Positive staining in the neuroendocrine component, negative in the adenocarcinoma component.

**Conclusion**

In 2010, WHO incorporated this rare entity of mixed adenoneuroendocrine carcinoma (MANEC) of the gallbladder in their classification. There are few isolated reports of the case; however, the clinical course of this tumor is unclear. Most published cases presented with a large mass. In our case, the carcinoma was confined in a polyp (lamina propria, pT1) yet followed an aggressive course with multiple recurrence / metastasis at unusual sites (abdominal wall and peritoneum). Locoregional spread into liver or lymph nodes which are usual in gallbladder carcinoma, was not seen.

**References**


