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clinical practice

Concomitant small cell carcinoma and adenocarcinoma of the gallbladder: a case report

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SUMMARY: **Concomitant small cell carcinoma and adenocarcinoma of the gallbladder: a case report.**

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Gallbladder cancer is the most frequent neoplasm originating from the extrahepatic biliary tract, with characteristics of late presentation and rapid progression. We report the case of a 58 years old female patient with concomitant small cell carcinoma and adenocarcinoma of the gallbladder, incidentally reported after a cholecystectomy performed for cholelithiasis. According to the stage of the disease, we performed a second surgical procedure with laparotomy, resection of the liver parenchyma IVb and V and regional lymphadenectomy. After multidisciplinary team consultation, the patient was not administrated chemotherapy. She was well followed up at our department and she is alive 12 month after surgery.

KEY WORDS: Neuroendocrine carcinoma - Gallbladder cancer - Surgical oncology.

Introduction

Gallbladder cancer is the most frequent neoplasm originating from the extrahepatic biliary tract. Most gallbladder cancer are adenocarcinomas (85%), followed by squamous, adenosquamous and neuroendocrine carcinoma. Neuroendocrine tumors account for 1.25% of all malignancies, with the majority (66%) occurring in the gastrointestinal tract, followed by bronchopulmonary system. Other less frequent locations include the ovaries, pancreas and hepatobiliary tree (1). We report the case of a patient with concomitant small cell carcinoma and adenocarcinoma of the gallbladder (GB), incidentally reported after a cholecystectomy performed for cholelithiasis. After the histological diagnosis, we performed a second surgical procedure with laparotomy, resection of the liver IV b and V segments and regional lymphadenectomy. After multidisciplinary team consultation and according to stage of the disease, the patient was not administrated chemotherapy and is alive 12 months after surgery.

Case report

A 58-year-old female was admitted with history of intermittent postprandial right upper quadrant pain radiating to the back, associated with nausea. Routine laboratory tests, including liver function tests, were all within normal limits. The US and CT images revealed a thick-walled gallbladder containing multiple stones (Figures 1, 2) Laparoscopic cholecistectomy was performed and, after an uneventful 48 hours postoperative recovery, the patient was discharged. On gross inspection, the gallbladder measured 11 cm in length and 4.5 cm in circumference. Three lesions were found at the histological examination: one of 2 cm in correspondence of the bottom, another one of 1.5 cm in correspondence of the body of gallbladder and another separate whitish yellow nodule measuring 2 x 1,5 cm. Histological examination revealed that the largest polypoid lesion was an intramucosal adenocarcinoma while the other one was a moderately differentiated adenocarcinoma (G2) infiltrating the

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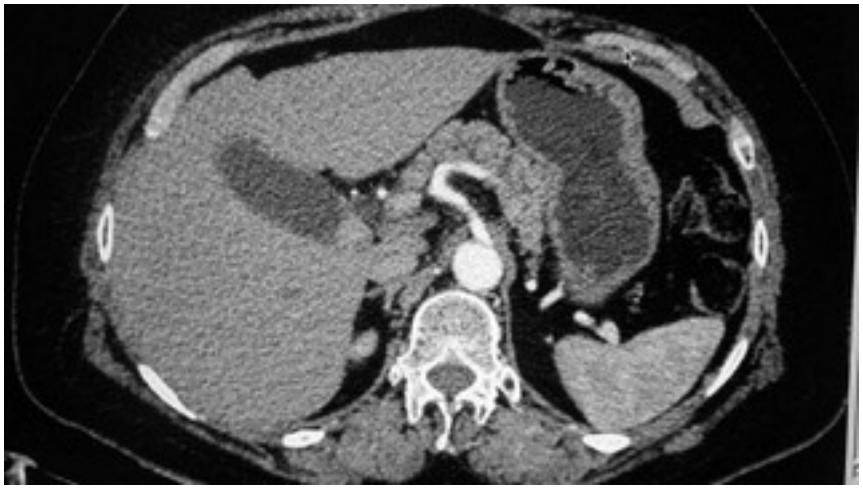

Figure 1 - Arterial phase of CT-scan.

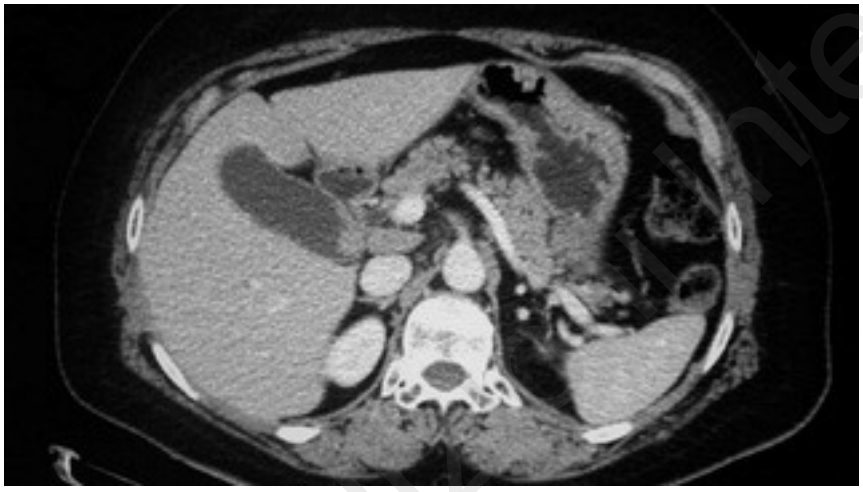

Figure 2 - Portal phase of CT scan.

wall of gallbladder, arised in a context of tubule-papillary adenoma with high-grade dysplasia. The analysis of one lymph node from surgical specimen, did not show focal metastatic deposits of neoplastic cells. (UICC VII edition: pT1b N0). The whitish yellow nodule was neuroendocrine carcinoma. Immunohistochemical studies revealed cells strongly positive for synaptophysin, CD 56 and chromogranin A. After a contrast enhanced CT scan, the patient underwent a second surgical procedure with resection of liver IVb and V segments with regional lymphadenectomy. Histological examination of liver parenchyma was negative from tumor. The patient had an uneventful postoperative recovery and, after multidisciplinary team consultation, was not administered chemotherapy. Twelve months after surgery, she is free from disease.

Discussion and conclusions

Neuroendocrine tumors (NETs) are rare neoplasms and arise from enterochromaffin cells, usually disposed in the mucosa of gastric and respiratory tracts. Neuroendocrine cells contain dense core secretory granules and lack axons and synapses and produce neurotransmitters, neuromodulators, or neuropeptide hormones. Neuroendocrine neoplasms (NENs) account for 1.25% of all malignancies, with the majority (66%) occurring in the gastrointestinal tract, followed by the bronchopulmonary system (31%). Other less frequent locations include the ovaries, pancreas, and hepatobiliary system (1). There have been several hypotheses about origin of GB NETs. First, neuroendocrine cells are seen only in the intestinal or gastric metaplastic GB mucosa, secondary to cholelithiasis

and chronic cholecystitis (2). Because of the expression of various neuroendocrine cells in this way, it is possible for NETs to occur. Secondly, it is possible that NETs may arise in ectopic pancreatic tissue in the gallbladder. The NETs comprise a heterogeneous group of neoplasms that vary from low-grade malignancy tumors to tumors with high malignancy. A recent classification published in 2010 by World Health Organization divides NETs into three categories (3): neuroendocrine tumor (NET), neuroendocrine carcinoma (NEC) and mixed adenoneuroendocrine carcinoma (MANEC). A NEC is composed of either small or large cells with marked nuclear atypia and a high proliferation fraction. NETs have a good prognosis, while NEC and MANEC have a poor prognosis. The incidence of the gallbladder carcinoma varies geographically and in different etnhic groups within the same country. In the USA was 0.9 per 100,000 males and 1.6 per 100,000 females, accounting for 0.16% and 0.39% of all cancer, respectively (4). The age at presentation has a range from 38 to 81 years (5) and a preoperative diagnosis of gallbladder small cell carcinoma (SCC) is difficult because of nonspecific symptoms and aspect at the ultrasonography, CT, or magnetic resonance imaging. Incidental diagnosis of gallbladder cancer on final pathology following a cholecystectomy for suspected benign biliary disease is the most common presentation and occurs following 0.25% of laparoscopic cholecystectomies (6). A macroscopically complete surgical excision with negative microscopic margins (R0) remains the only potentially curative treatment for gallbladder cancer. The extent of resection depends of the T-stage of the tumor. In T1a stage, a simple cholecystectomy alone has been accepted as the gold standard; in advanced T-stage, according to the recommendation of the National Comprehensive Cancer Network (NCCN), the treatment includes extended cholecystectomy with en bloc resection of adjacent liver IVb and V segments and regional lymph node dissection (7, 8). In unresectable tumors, the primary management is chemotherapy with cisplatin, etoposide, and 5-fluorouracil. Few papers showed specific chemotherapy regimens (9, 10). The role of radiotherapy remains undefined due to paucity of data (9).

Cases of gallbladder neuroendocrine cell carcinoma coexisting with adenocarcinoma are extremely rare, with about 150 cases reported in the literature. Neuroendocrine carcinoma has an high tendency to invade the adjacent hepatic tissues and give early lymph node and distant metastases, vessel invasion resulting an exceedingly poor prognosis even after curative resection. The prognosis of NEC associated with poorly differentiated adenocarcinoma becomes even worse. In our study, we present a concomitant small cell neuroendocrine carcinoma and adenocarcinoma of the gallbladder, incidentally reported after laparoscopic cholecystectomy. We performed extended resection of IV b and V liver segments and regional lymphadenectomy. The patient is alive 12 month after diagnosis. We think that an increased awareness of the biological features and treatment option of this tumor is required to improve prognosis.

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