

Neuroendocrine Tumors of the Gallbladder: A Case Report and the Management of Diagnosis and Treatment

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Neuroendocrine tumors of the gallbladder (NET) account for 0.5% of all neuroendocrine tumors and 2% of the gallbladder (GB) cancers. The symptoms of GB-NETs are nonspecific and the diagnosis is made preoperatively at the time of cholecystectomy for cholelithiasis. The main treatment for these tumors remains surgery. The role of adjuvant therapy after complete resection is undefined, whereas in metastatic disease some chemotherapeutic drugs besides Sandostatin or interferon alpha (IFN) have some activity. Here we report a case of a 69 year old female who underwent emergency laparoscopy for a diagnosis of acute lithiasic cholecystitis. Macroscopic examination of the gallbladder revealed the presence of an intraluminal tumoral mass and histopathological investigation concluded the diagnosis of a carcinoid tumor of the gallbladder. Post-operative evaluation completed by serologic detection of neuroendocrine markers and imaging established the diagnosis of a locally advanced gallbladder neuroendocrine tumor. The patient received 6 cycles of chemotherapy, associated with Sandostatin, with partial tumoral response. After 12 months, under maintenance treatment with Sandostatin, the disease progressed loco-regionally. We reinitiated chemotherapy with XELOX regimen, and elevated the doses of Sandostatin. After 4 cycles of treatment the patient is once again in partial remission.

Key words: neuroendocrine, gallbladder, tumor, carcinoid, chemotherapy, cholecystitis, cholecystectomy, somatostatine, immunohistochemistry, PET-CT

Introduction

Neuroendocrine tumors (NETs) represent a rare group of malignancies derived from Kulchitsky cells. The most common affected sites are the gastrointestinal and bronchopulmonary tracts. Gallbladder NETs represent 2% of all NETs (1). The first carcinoid tumor was described in 1888, while the first carcinoid tumor of the gallbladder was reported by Joel in 1929 (2). These tumors are usually diagnosed at an advanced stage having a very aggressive biological behavior. There are no specific signs or symptoms for this group of tumors and the diagnosis is usually incidental, during surgery for a suspected gallstone-related disease. We herein describe a case of a classical gallbladder carcinoid diagnosed in a 69 year-old woman.

Case report

A 69-year old woman from an urban area, with a 10-year history of vesicular lithiasis, was admitted to the hospital

complaining of right upper quadrant pain, chills, nausea and inapetence. The symptoms debuted about 24 hours prior to presentation and had intensified progressively. Physical examination revealed right upper abdominal quadrant during palpation and positive Murphy's sign. Laboratory studies showed increased total and direct bilirubin values (TB=8mg/dl, DB=5 mg/dl). Gallbladder wall thickening was documented using ultrasonography, but no images of stones, biliary dilatation or polyps were captured. The case was preoperatively interpreted as acute lithiasic cholecystitis and a laparoscopic cholecystectomy was performed. On gross inspection, the GB presented an irregular, friable endoluminal green mass. Microscopy revealed a malignant tumor, infiltrating the corion, musculosa and the subserous layer (Fig 1a). Immunohistochemistry revealed positivity for chromogranin A (Fig 2a), synaptophysin (Fig 2b), CK AE1/AE3; CK7 was positive only for some tumor cells; CK20 coloration was negative; the proliferation index (Ki-67 coloration) was 50% (Fig 1b). Histopathological investigation and immunohistochemistry concluded the presence of a carcinoid tumor of the gallbladder.

Post-operatively, one month after surgical recovery, our patient had g/L), normal serum level μ elevated serum levels of chromogranin A (101 of serotonin and elevated urinary level of 5-hidroxi-indolacetic acid (14,4 mg). Abdominal

and pelvic CT scan described no pathological images. This determined us to perform an 18 F-FDG PET/CT, in order to check for distant metastasis. PET-CT discovered three hypermetabolic tumoral nodules in the right lumbar region, 15-17 mm in size. We performed an abdominal MRI with liver-specific contrast agent- gadoxetic acid (Gd-EOB-DTPA, Primovist), showing a mass with cystic and solid components in the subhepatic space (Fig 3a, 3b). The case was interpreted as locoregional tumor progression and, due to the high proliferation index and early locoregional relapse, we decided on the initiation of chemotherapy.

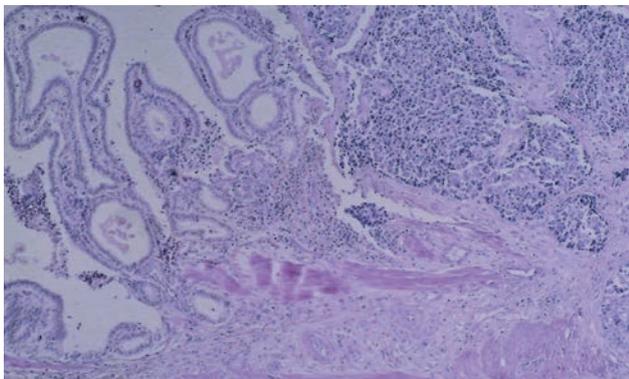


Fig. 1a. Microscopic aspect of the malignant tumor

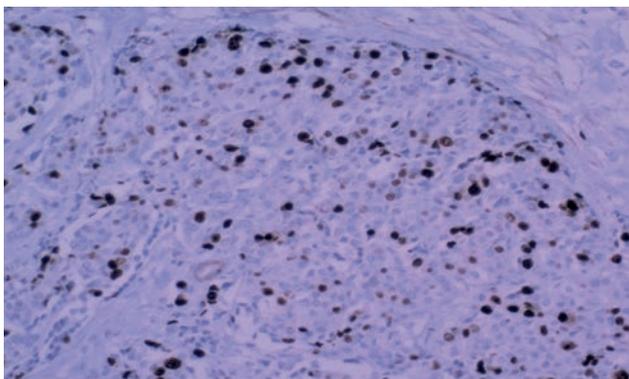


Fig. 1b. Ki-67 coloration

The patient subsequently underwent 6 cycles of palliative chemotherapy comprising Etoposide (100 mg/m²), on day 1-3 and Cisplatin (60 mg/m²) on day 2. Sandostatin LP 20 mg was associated from the 3rd cycle of chemotherapy for the carcinoid syndrome. An abdominal Primovist-enhanced MRI performed after chemotherapy (Fig 4a, 4b) revealed partial tumoral response (reduction over 50% of tumor mass).

Chemotherapy was interrupted due to the patient's low tolerance, but Sandostatin treatment continued. After 12 months, under maintenance treatment with Sandostatin, the disease progressed loco-regionally. We reinitiated chemotherapy with XELOX regimen, and elevated the doses of Sandostatin. After 4 cycles of treatment the patient is once again in partial remission.

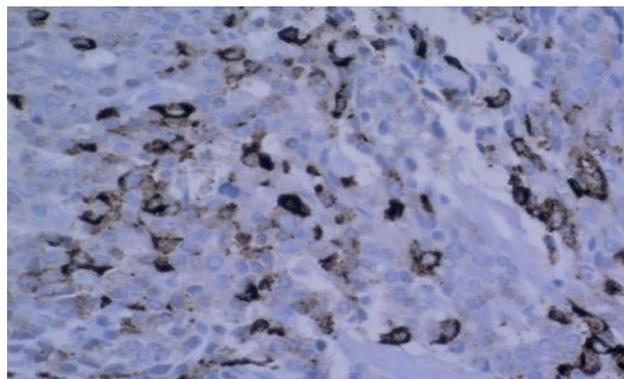


Fig. 2a. Chromogranin A- positive immunohistochemistry

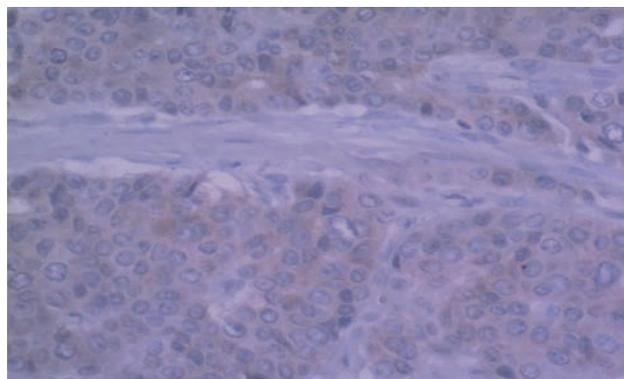


Fig. 2b. Synaptophysin- positive immunohistochemistry

Discussions

NETs in the gallbladder account for 0.5% of all NET and 2% of the gallbladder cancers (1). Neuroendocrine cells usually do not exist in the normal gallbladder, occurring only in intestinal or gastric metaplastic gallbladder mucosa, seen secondary to cholelithiasis and chronic cholecystitis (3). GB-NETs symptoms are nonspecific, including upper abdominal pain, discomfort, jaundice, their diagnosis being made preoperatively at the time of cholecystectomy for cholelithiasis. The presence of the carcinoid syndrome is very rare (<1%) (4). The case reported here was initially diagnosed as acute lithiasic cholecystitis, on the basis of clinical presentation and ultrasound examination (US). The curative treatment for neuroendocrine gallbladder cancer is surgical. The lack of surgery strategy is explained by the rarity of the disease and limited knowledge regarding the biology of the lesion. Re-exploration after laparoscopic cholecystectomy reveals that 74% of patients have residual disease, whereas the majority of patients who have undergone a potentially curative resection for NET-GB by an aggressive surgical approach will develop metastatic disease (5). Assessments of the tumor proliferation index (Ki67), presence of mucin, penetration of the serosa are necessary to define the surgery strategy (5). For many years, serum level of chromogranin A, serotonin, and their urinary metabolite 5-HIAA have been the standard for detecting and following

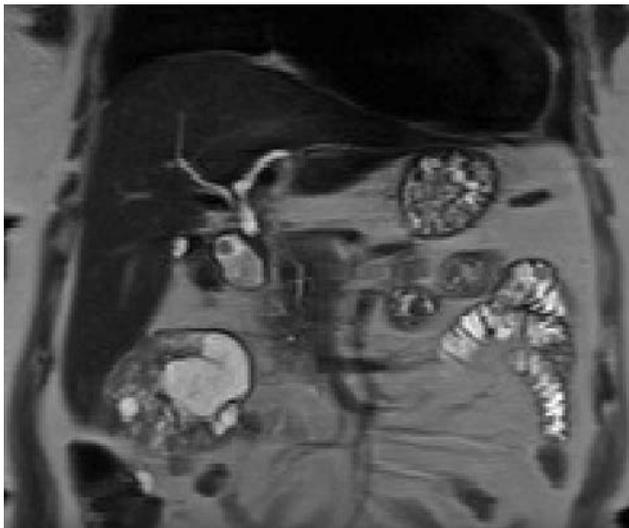


Fig. 3a. Abdominal MRI with liver-specific contrast agent, before chemotherapy: mass with cystic and solid components in the subhepatic space

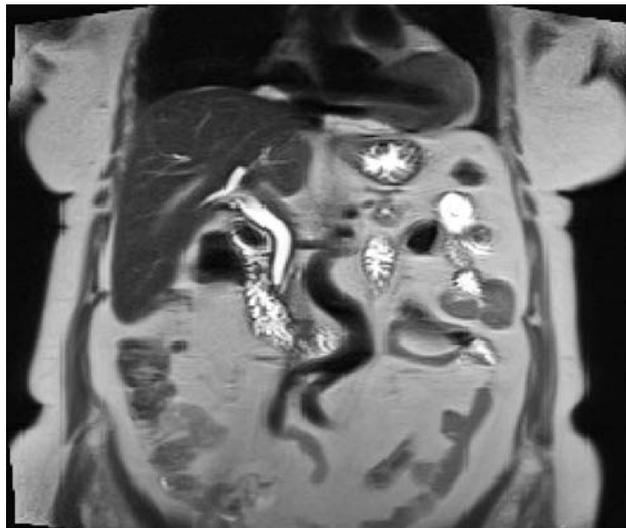


Fig. 4a. Abdominal Primovist- enhanced MRI, after chemotherapy: partial tumoral response



Fig. 3b. Abdominal MRI with liver-specific contrast agent, before chemotherapy: mass with cystic and solid components in the subhepatic space

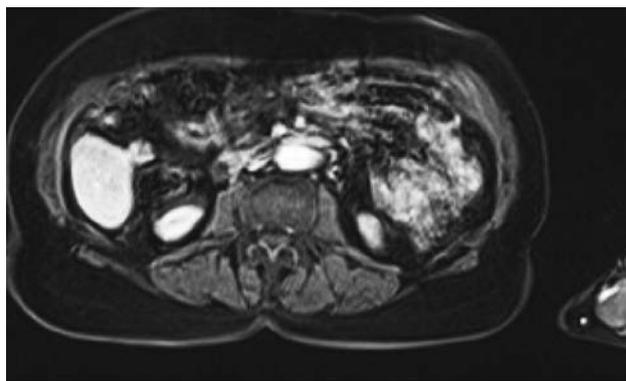


Fig. 4b. Abdominal Primovist- enhanced MRI, after chemotherapy: partial tumoral response

carcinoids tumors. The serum level of these markers depend upon tumor mass, tumor burden, their sensitivities and specificities for the detection of NETs ranging between 70% and 100% (6, 7). Regarding the imaging of the NETs, several modalities have been widely used including sonography, computer tomography (CT), magnetic resonance imaging (MRI), positron emission tomography [F]- fluorodeoxyglucose (FDG) and somatostatin receptor scintigraphy (SRS) (8). CT and MRI are useful methods for the staging and localization of solid tumors, including NETs. A contrast medium should be used in performing these methods. Detection of hepatic metastases is higher in MRI than CT. Gadoxetic acid (Gd-EOB-DTPA, Primovist) is a liver-specific MRI contrast agent that significantly improves detection of focal liver lesions compared to CT and standard MRI, being rapidly distributed through the bloodstream with high liver-specificity (9). Because of their generally lower proliferative activity, positron emission tomography [F]- fluorodeoxyglucose (FDG) imaging has

low sensitivity in well-differentiated NETs (10). Other new PET imaging agents such as ^{18}F -FDOPA, ^{68}Ga -DOTA-TOC, ^{68}Ga -DOTA-NOC and ^{18}F -FPGLUC-TOCA have a higher sensitivity for NET (11, 12). Somatostatin receptor scintigraphy (SRS) – ^{111}In -pentetreotide scintigraphy is a useful tool for imaging carcinoid tumors, with a high affinity for somatostatin subtype 2 and 5 receptors present on the cell membranes of carcinoid tumor cells, seen in 80 – 90% of NETs (16). The overall sensitivity of [^{111}In -DTPA0] octreotide scintigraphy is 80- 90% (13). The role of radiotherapy and chemotherapy in the management of this disease is unclear. In adjuvant setting ,after complete tumor resection, chemotherapy is not effective (14). In metastatic disease, the Ki-67 proliferation index is an important factor for therapeutic management (15). According to the Ki67 index, the patients with high proliferation index should receive chemotherapy, while patients with low proliferation index should be treated with somatostatin analogues and interferon (IFN). Chemotherapeutics such as Dacarbazine,

Mitoxantrone, Paclitaxel, Irinotecan, Oxaliplatin, 5 Fluorouracil (5FU), Doxorubicin, have shown a response rate between 5% to 30%, the most effective combinations being Streptozotocin + 5FU+ Doxorubicin (RR=39%), Oxaliplatin + Capecitabine (RR=30%), Irinotecan + FU (16). Somatostatin is a native hormone involved in the regulation of several systems and tissues, acting on five somatostatin receptors subtypes (sst 1-5). Octreotide was the first synthetic somatostatin analogs developed which binds with high affinity to sst 2 and with lower affinity to sst 3 and sst5 (17). Lanreotide (LAR), another cyclic analog has similar affinity and activity profile as octreotide. The PROMID study has recently demonstrated the anti-tumoral effect of octreotide LAR even in sst negative patients (18). Alpha interferon has been used in the treatment of NETs, with low proliferation index, symptomatic and biochemical response being seen in 50% of patients with tumor reduction in 10-15%. Combined therapy with IFN and somatostatin analogues may have an additive effect on inhibiting tumor growth (19). Chemotherapy may be a second line option in tumors which progress rapidly when on biotherapy. Although therapeutic options are available when detected at an early stage, the prognosis for these tumors is very poor, with a 5-year survival rate of less than 10%.

In **conclusion**, we reported a case of neuroendocrine tumor of gallbladder diagnosed as acute lithiasic cholecystitis, with a good response to chemotherapy and analogs of somatolines.

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