Primary neuroendocrine tumors of the gallbladder: Ultrasonographic and MDCT features with pathologic correlation

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Histologically adenocarcinomas represent 95% of all gallbladder carcinomas [1]. Conversely, primary neuroendocrine tumors of the gallbladder are extremely rare, representing 0.2% of all neuroendocrine tumors and only 2% of all gallbladder carcinomas [2]. The diagnosis of primary neuroendocrine tumors of the gallbladder is usually made during histopathological analysis because no suggestive imaging features that allow discriminating between this specific tumor and the more common gallbladder adenocarcinoma have been described [3]. Because of its rarity, the imaging features of primary neuroendocrine tumor of the gallbladder have received little attention so far.

We report herein the ultrasonographic and multidetector row computed tomography (MDCT) findings of two cases of histopathologically confirmed primary neuroendocrine tumors of the gallbladder that presented as large gallbladder masses in association with large metastatic lymph nodes and intrahepatic metastases.
Case 1

A 55-year-old man was referred to us because of non-specific abdominal pain. He also complained of weight loss. He had no remarkable prior history. Physical examination showed mild jaundice and a palpable mass in the right upper quadrant of the abdomen.

Laboratory tests showed low serum albumin level (4.4 g/dL; normal value, 65—78) and elevated aspartate aminotransferase (AST) (162 IU/L; normal value: 10—50), alanine aminotransferase (ALT) (189 IU/L; normal value: 10—50), alkaline phosphatase (255 IU/L; normal value: 38—115), total bilirubin (57.3 μmol/dL; normal value < 17 μmol/dL) and gamma glutamyl transpeptidase (1098 U/L; normal value < 55) levels. Levels of tumor markers were elevated for carbohydrate antigen (CA) 19—9 (79.9 μg/mL).

Ultrasoundographic examination of the abdomen revealed the presence of a 4-cm mixed echogenic mass in segment 4 of the liver and an 8.5-cm mass in the fundus of the gallbladder. No stones were visible in the gallbladder mass. No biliary dilatation was noted and there was no ascites. MDCT of the abdomen showed an 8.5 × 6 cm exophytic, heterogeneous mass in the fundus of the gallbladder (Fig. 1). There were two large necrotic lymphadenopathies in the porta heparis and retroportal space.

The patient was operated on and intraoperative exploration showed a large gallbladder mass that involved the segment 4 of the liver and a large lymph node of the porta heparis. The tumor was found to involve the transverse mesocolon. A complex surgical resection was performed consisting in resection of segments 4, 5 and 6 and right colon. The patient further received systemic chemotherapy consisting in VP-16 and cisplatin.

After surgical resection histopathological analysis revealed that the tumor was composed of monomorphic cells containing small, round nuclei and eosinophilic cytoplasm. Cells were organized in small nodular, trabecular, or acinar structures surrounded by a richly vascularized stroma in association with multiple mitoses. Immunohistochemical analysis revealed that the cells were negative for cytokeratin, vimentin, and CD-45 but positive for CD 56, chromogranin A, synaptophysin and Ki 67 (90%). The same findings were observed on resected lymph nodes and intrahepatic lesions. These findings were consistent with the diagnosis of small cell neuroendocrine carcinoma of the gallbladder with hepatic and lymph node involvement. The TNM classification of the tumor was T3 N1 M1.

Case 2

A 64-year-old woman was referred to us because of abdominal pain and jaundice. She also complained of anorexia and a weight loss of 5 kg during the previous month. Her prior history was remarkable for type 2 diabetes, infiltrative breast adenocarcinoma treated by surgical resection and non-alcoholic steatohepatitis (NASH). Physical examination showed mild jaundice. No palpable mass of the abdomen was found.

Laboratory tests showed elevated AST (134 U/L; normal value: 10—50), ALT (126 IU/L; normal value: 10—50), alkaline phosphatase (350 IU/L; normal value < 115), total bilirubin (235 μmol/dL; normal value < 17 μmol/dL), and gamma glutamyl transpeptidase (1098 U/L; normal value < 55) levels. Levels of tumor markers were elevated for CA 19—9 (771 μg/mL) but not for carcinoembryonic antigen.

Ultrasoundographic examination of the abdomen revealed the presence of large, heterogeneous mass measuring 75 × 67 mm that appeared to originally develop from the gallbladder in association with two echogenic masses in segment 4 of the liver (Fig. 2). Stone was visible in the gallbladder mass. Biliary dilatation in the left hemiliver was present. MDCT of the abdomen confirmed presence of a heterogeneous mass of the gallbladder measuring 82 × 65 mm in association with two hepatic metastases of 3- and 4-cm in largest axial diameter and one large heterogeneous necrotic lymphadenopathy in the porta heparis.

Percutaneous biopsy was performed and histopathological analysis revealed high grade neuroendocrine carcinoma of the gallbladder with hepatic metastases. Immunohistochemical analysis revealed that the tumor cells were negative for cytokeratin, vimentin and CD-45 but positive for CD 56, chromogranin A, synaptophysin and Ki 67 (100%), thus excluding liver metastasis from breast carcinoma.

The patient was denied surgery. She received palliative therapy in the form of endoscopic biliary stent placement and chemotherapy including VP-16 and cisplatin. Follow-up MDCT examination revealed complete tumor response three months later.

Discussion

Papers reporting cases of primary neuroendocrine tumors of the gallbladder have not placed a special attention to the imaging findings of this specific subgroup of gallbladder tumor. In some reports, the tumor itself was not visible at imaging and was found incidentally during histopathological analysis of resected specimen after surgical resection of the gallbladder for another reason that the tumor itself [4—6]. In other cases, the tumor presented as an irregular, circumferential thickening of the gallbladder [2] or as an intraluminal polypoid mass [2, 3, 7] similar to the findings observed in the more common adenocarcinoma of the gallbladder [6, 8]. Primary neuroendocrine tumors of the gallbladder may also present as chronic cholecystitis with circumferential, homogeneous thickening of the gallbladder wall with intraluminal stones [9]. Finally, primary neuroendocrine tumor of the gallbladder may present as a large gallbladder mass, which is also a finding similar to the more common gallbladder adenocarcinoma as observed in our two patients [10].

The most frequent MDCT finding in gallbladder adenocarcinoma at initial presentation is a mass that fills more of 50% of an enlarged and deformed gallbladder and that is often exophytic [8, 11]. The mass is typically hypoattenuating and shows variable degrees of enhancement. The second most common presentation is a polyloid intraluminal mass greater than 1-cm in diameter [11]. Finally, gallbladder adenocarcinoma can present as a symmetric or an asymmetric gallbladder wall thickening that may be similar to that observed in chronic cholecystitis [11]. Clinically, bile duct obstruction is present in 25% of patients with gallbladder cancer [12].
Figure 1. Fifty-five-year-old man presenting with non-specific abdominal pain and weight loss: a: MDCT of the abdomen in the axial plane after intravenous administration of iodinated contrast material shows heterogeneous mass (arrow) in the fundus of the gallbladder in association with large, heterogeneous lymphadenopathies (arrowheads) in the porta hepatis and retroportal space; b: MDCT of the abdomen in the coronal plane shows a large, heterogeneous mass (arrows) in the fundus of the gallbladder. Intrahepatic metastasis (arrowhead) is visible; c: photograph shows resected gross specimen of enlarged metastatic lymph nodes of porta hepatis; d: hematoxylin and eosin section shows poorly differentiated neuroendocrine carcinoma made of monomorphic cells with small and round nuclei and eosinophilic cytoplasm with serosal and liver invasion (magnification ×10); e: immunohistochemical staining shows a Ki-67 index (i.e., proliferation index) over 90%.

In our two patients, MDCT showed a large, infiltrative mass with associated enlarged lymph nodes at the porta hepatis in both patients and in the retrocaval space in one of them. MDCT findings were suggestive for the diagnosis of gallbladder adenocarcinoma. The final diagnosis was made after histopathologic analysis similar to prior cases reported in the literature [2,3,9,10]. Of interest, in both patients, the metastatic lymph nodes were abnormally enlarged, which is a finding that has not been reported neither in previous cases of primary neuroendocrine tumors of the gallbladder nor in the most common gallbladder adenocarcinoma.
Lymph node metastases are present in 25% to 80% of cases of gallbladder adenocarcinomas [13]. The gallbladder drains to the superior pancreaticoduodenal lymph nodes via cystic, pericholedochal and retroportal lymph nodes and then to the interaortocaval lymph nodes [1,8]. Direct extension involves segment 4 followed by segment 5 of the liver and can be responsible for capsular retraction of the adjacent liver [14].

Therapeutic options for primary neuroendocrine tumors of the gallbladder are often limited due to the advanced nature of the disease at diagnosis. Surgical resection when possible remains the best option for cure [15]. However, the need for radical resection is still debated [15,16]. Because of the rarity of this disease, no definite treatment has been clearly defined. Adjuvant chemotherapy is often used but there is no well-defined protocol. Effective treatment options are currently limited to complete surgical resection with negative margins [15]. Among our two patients, only one was amenable to extended curative resection including atypical partial hepatectomy with chemotherapy whereas the other received palliative therapy only after the diagnosis was obtained after percutaneous biopsy [17].

Histopathologically, primary neuroendocrine tumors of the gallbladder are predominantly poorly differentiated neuroendocrine tumors [2,3,9]. The definite diagnosis is based on immunohistochemical expression of marker proteins. In our two patients, immunohistochemical analysis showed that tumor cells were negative for cytokeratin and vimentin and positive for CD 56, chromogranin A and synaptophysin, thus supporting the final diagnosis of neuroendocrine tumor [2,3,9].

In conclusion, we have reported the ultrasonographic and MDCT findings in two patients with primary neuroendocrine tumors of the gallbladder. This specific tumor presents as large heterogeneous gallbladder masses that are similar to the more common gallbladder adenocarcinoma. Our observations may suggest that the presence of markedly enlarged metastatic lymph nodes might be a discriminating feature to differentiate between primary neuroendocrine tumor and the more common adenocarcinoma of the gallbladder on imaging. However, this assumption should be validated by further comparative case-control studies.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References