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CASE REPORT

GALLBLADDER NEUROENDOCRINE TUMOUR – AN ACCIDENTAL DISCOVERY

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Abstract

Introduction. Primary neuroendocrine tumours of the gallbladder represent 0.2% of all neuroendocrine tumours. The diagnosis is incidental in most cases.

Case report. We present the case of a male patient, with no significant personal pathological history, who presented for pain in the right hypochondrium with posterior irradiation. The abdominal ultrasound examination performed at presentation in the emergency room described an acute lithiasis cholecystitis. Laparoscopic surgery proved difficult due to adhesions and difficulties in grasping the gallbladder. The results of the histopathological examination established the diagnosis of a small cell neuroendocrine carcinoma, confirmed by the immunohistochemical tests.

Conclusions. In most cases of primary neuroendocrine tumours of the gallbladder the paraclinical examinations suggest a benign disease. The positive diagnosis is done after surgery, by histopathological examination, which can change the postoperative therapeutic management.

Keywords: neuroendocrine tumour, gallbladder, laparoscopic cholecystectomy.

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Résumé

Tumeur neuroendocrine de la vésicule biliaire – une découverte fortuite

Introduction. Les tumeurs neuroendocrines primitives de la vésicule biliaire représentent 0,2% de toutes les tumeurs de ce type.

Rapport du cas. On vous présente le cas d'un patient de sexe masculin sans antécédents significatifs personnels pathologiques, qui s'est présenté dans notre clinique accusant des douleurs dans l'hypochondre droit à réponse postérieure. L'échographie abdominale effectuées à la présentation montrait l'image d'une cholécystite aigue lithiasique. L'intervention chirurgicale laparoscopique s'est avérée difficile à cause d'adhérences et difficultés de serrer la vésicule. Les résultats de l'examen histopathologique ont établi le diagnostic de carcinome neuroendocrine à petite cellule, confirmé par l'examen de l' immunohistochimie.

Conclusions. Dans la plupart des cas de tumeurs neuroendocrines primitives de la vésicule biliaire, les examens paracliniques suggèrent une maladie bénigne. Le diagnostic positif histopathologique en post-opératoire

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Introduction

Carcinoids are rare, low-volume neuroendocrine tumours derived from enterochromatophin or Kulchitsky cells that are distributed throughout the body[1-3]. Therefore, neuroendocrine tumours can be found anywhere in the body, especially in the gastrointestinal tract (67%), followed by the bronchopulmonary tract (25%)[4]. These are distinct histological entities that can range from asymptomatic neoplasms to aggressive, metastatic neoplasms.

Gallbladder carcinoma is among the five most common gastrointestinal malignancies[5]. Among the risk factors there are stones larger than 3 cm, main bile duct cysts and chronic inflammation[5]. The neuroendocrine type of biliary adenocarcinoma is an extremely rare malignancy, being encountered in 0.2% of malignant tumours of the gastrointestinal tract[1]. This malignancy mainly affects the female population in the 6-7th decade of life. It is often discovered late, when accompanied by mechanical obstruction, and the prognosis is reserved, having significantly lower survival rates compared to other malignant diseases of the gallbladder.

Case presentation

A 71-year-old male patient was admitted to the surgery clinic on September 22, 2011 for pain in the right hypochondrium with posterior irradiation, and biliary dyspeptic syndrome. The patient reports that the symptoms started insidiously 5 days before and progressively worsened. The patient was known with therapeutically neglected primary arterial hypertension and cerebellar atrophy, detected by computed tomography examination in 2006. From the family history, the patient reports that his father underwent cholecystectomy at the age of 70 years. After cholecystectomy, his father underwent another surgical intervention that resulted in the excision of a "part of the liver" and died of natural causes 15 years later.

The patient has a medium general condition at admission, with no fever. The clinical examination revealed hollowed abdomen, spontaneous pain and palpation in the right hypochondrium, positive Murphy's sign. In the right groin region, there was a mass of about 3/2 cm, oval in shape, soft in consistency, painless to touch, reducible to taxis with cough impulse. The patient had reduced digestive tolerance, with bilious vomiting, slowed intestinal transit.

The laboratory tests revealed leucocytosis (13,110/mm^3), alanine aminotransferase (ALT) 77 IU/L, aspartate aminotransferase (AST) 64 IU/L, fibrinogen 723 mg/dL, hemoglobin 11.7 g/dL, glucose 116 mg/dL, alkaline phosphatase 160 IU/L.

The ultrasound examination detected the gallbladder with thickened walls (8-9 mm), with minimal fluid, multiple stones inside, normal intrahepatic ducts, normal common bile duct (7mm), with no other pathological findings.

Considering the patient's symptomatology, corroborated with the paraclinical investigations, after preoperative preparation, laparoscopic emergency surgery was decided. Intraoperatively, a subhepatic plastron, that includes the gallbladder, large omentum, right colon and duodenum, was found, for which complete difficult laparoscopic adhesiolysis was performed. The gallbladder was distended, with a thickened wall; the puncture of the gallbladder was performed, with extraction of turbid bile and pus, followed by retrograde laparoscopic cholecystectomy, peritoneal lavage and subhepatic drainage. The gallbladder was extracted after widening the epigastric operative trocar orifice, requiring the closure of the musculoaponeurotic fascia with non-resorbable sutures.

At the macroscopic examination in the operating room, the gallbladder had dimensions of 100/60 mm and multiple microcalculi, the largest having a diameter of approximately 1 cm. A white polypoid mass, with a diameter of approximately 15 mm, was found inside and at the level of the serosa another similar mass was detected.

The postoperative evolution was favorable, with suppression of the drainage tube after 2 days. The wounds healed "per primam", the patient had a good digestive tolerance and intestinal transit resumed, being discharged on the 4th day postoperatively.

maneuver, donne la certitude et peut modifier l'approche thérapeutique postopératoire.

Mots-cles: tumeur neuroendocrine, vésicule biliaire, cholécystectomie laparoscopique.

The macroscopic histopathological examination revealed the gallbladder with thickened wall, increased consistency, hemorrhagic mucosa and erosions. At the level of the body, a tumour with polynodular appearance was identified, with a diameter of 23 mm, located in the wall, extended submucosally and predominantly towards the surface of the gallbladder, with a firm, yellow section (Fig.1.)

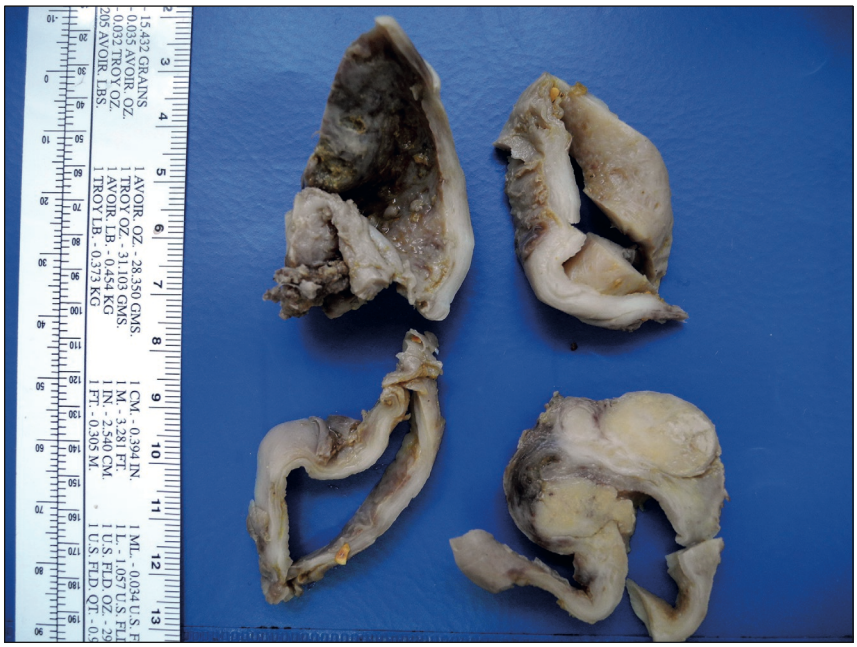

Fig.1. Macroscopic appearance, fixed surgical specimen.

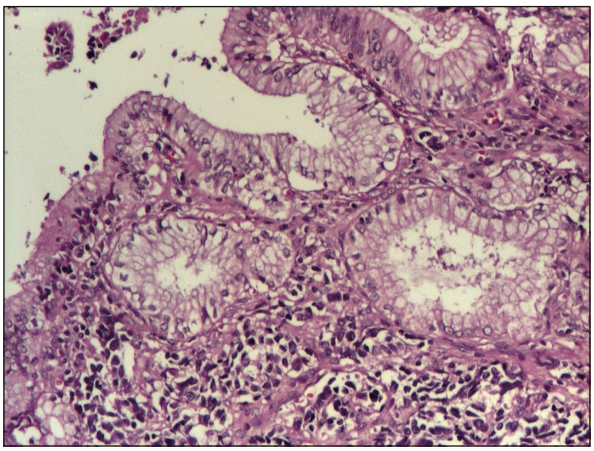

Fig.2. Haematoxylin and eosin staining colour:

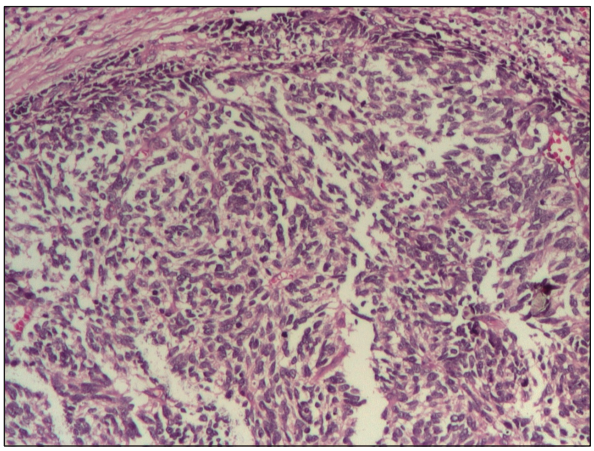

Fig. 3. Haematoxylin and eosin staining: compact tumor proliferation invasion of the gallbladder mucosa

The microscopic examination showed a tumour proliferation with cells of relatively uniform size, medium/ small size, arranged in anastomosed beaches, solid nests, occasionally in islands/ anastomosed trabeculae, which infiltrate the mucosa, muscle tunica and extends into the serosa. No glandular differentiation was identified. Tumour cells show weak eosinophilic cytoplasm, nuclei with slight pleomorphism, round-oval, hyperchromic, with coarse chromatin, without identifiable nucleolus (Fig. 2, 3).

To establish the definite diagnosis, the immunohistochemical examination is required. The immunohistochemical analysis reveals tumour cells with intense reaction to chromogranin (Fig. 4) and synaptophysin (Fig. 5); the Ki67 proliferation index (Fig. 6) was 50% of the tumour cells. Cytokeratin 7 (Fig. 7)

was positive in the tumour, and cytokeratin 20 focal, both with granular paranuclear reaction. CDX2 transcription factor was identified with poor expression in a small tumour population.

The conclusion of the immunohistochemical examination stands in a small cell neuroendocrine carcinoma (World Health Organization classification 2010), pleading for the primary biliary origin.

The interdisciplinary oncological and endocrinological consultations did not recommend complementary chemotherapy, but only follow-up. The patient returned to control 60 days postoperatively, without any clinical manifestations. Laboratory and imaging investigations (abdominal ultrasound, abdominal and chest computed tomography) did not detect tumour recurrence.

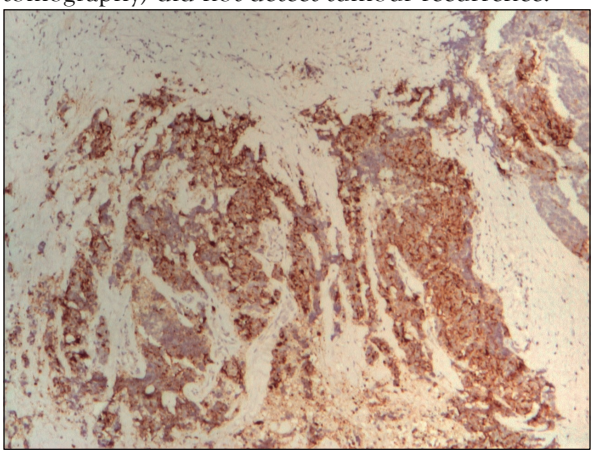

Fig. 4. Immunohistochemistry. Synaptophysin – diffuse reaction

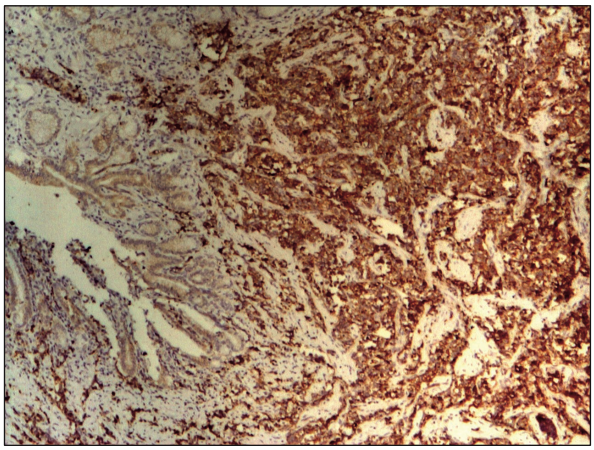

Fig. 5. Immunohistochemistry. Chromogranin – diffuse reaction

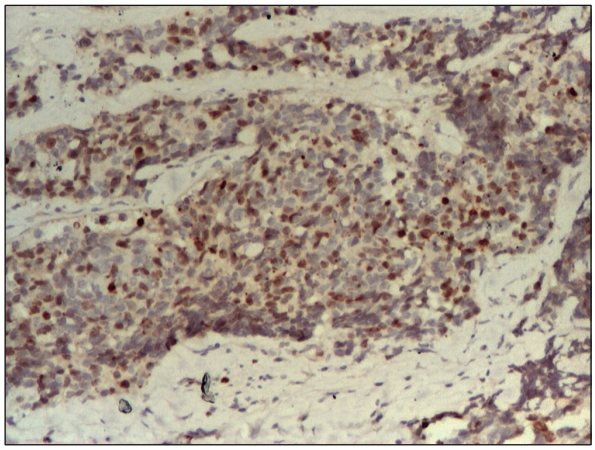

Fig. 6. Immunohistochemistry, Ki 67.

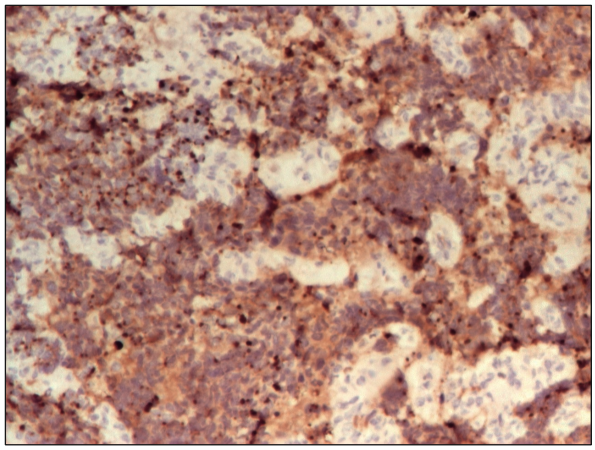

Fig. 7. Immunohistochemistry, Cytokeratin 7.

The re-evaluation of the patient 6 months postoperatively, in the endocrinology clinic, revealed 5-hydroxy-indoleacetic acid (5 HIAA) 3.8 mg/24h (2-9mg/24h), chromogranin A 77 μg/L (27-94μg/L), and serum serotonin 128 μg/L (80-400 μg/L). The markers were sent to a laboratory abroad (Germany) for analysis. Thoracic and abdominopelvic computed tomography did not find signs of tumour recurrence, no metastasis, supra- or subdiaphragmatic lymphadenopathy were found.

The patient presented to another control 12 months postoperatively, without clinical or paraclinical signs of recurrence. After this date, he did not show up for the scheduled check-ups.

Discussion

The embryological development of the liver and extrahepatic bile ducts begins in the middle of the 3rd week of intrauterine life when the hepatic diverticulum is formed from the endoderm of the distal portion of the proenteron. It develops in the thickness of the transverse septum. The connection between the hepatic buds and the proenteron is elongated and narrowed to form the bile duct. The gallbladder and cystic duct result from an evagination at the ventral wall of the bile duct. It has initially a tubular structure, later undergoing

morphological changes, to become saccular in the 11th week of intrauterine life[6].

The diagnosis of gallbladder neuroendocrine tumour cannot be established preoperatively, because the patient's symptoms at the time of presentation are usually nonspecific, such as upper abdominal discomfort and pain, jaundice and weight loss. According to the latest studies, the existence of carcinoid syndrome is very rare (<1%) and most neoplastic lesions are accidentally discovered intraoperatively[1]. In the literature, there are presented cases of association of carcinoid syndrome with acute cholecystitis.

Carcinoid is a malignant tumour that develops from silvery cells in the digestive tract, trachea, bronchi, excretory tract of the pancreas and liver. These cells are programmed for endocrine functions. 42 such cases have been reported so far[7]. The first case of a biliary neuroendocrine tumour was reported by Joel in 1929[8]. The risk of a person with a first-degree relative with a neuroendocrine tumour is four times higher than that of the general population. 20% of these patients develop another common digestive neoplasm during their lifetime[8].

Primary neuroendocrine tumours of the gallbladder are very rare, as no neuroendocrine cells are found in the normal mucosa of the gallbladder. However, chronic inflammation can induce mucosal metaplasia, with the detection of neuroendocrine cells at this level. These peculiar tumours are divided into secretory and non-secretory. The secretory tumours can produce serotonin, histamine, prostaglandins, vaso-intestinal polypeptide (VIP), glucagon. Gallstones may be secondary to pancreatic polypeptide secretion. Neuroendocrine carcinomas are aggressive tumours with a poor prognosis. Their cells are positive for nuclear cell proliferation antigen. Although there are many investigations to explore the bile ducts, such as cholangio-magnetic resonance imaging, the best test for diagnosing a biliary localized neuroendocrine tumour is scintigraphy for somatostatin receptors[9-11].

Regarding the treatment, chemotherapy may be effective, especially in small neuroendocrine cell carcinomas.

If the pathological examination reveals the presence of a neuroendocrine tumour, certain factors must be carefully analyzed, such as Ki67 level, mitosis index, mucin presence, serous penetration, tumour infiltration of liver tissue, tumour infiltration of lymph nodes, factors that influence the need for a new surgical intervention (lymphadenectomy and hepatic resection)[12,13].

Regarding the prognosis of this type of neoplasia, it is not possible yet to estimate accurately, because the data provided by the few cases published in the literature are often incomplete. Specific prognostic factors have not been identified for gallbladder carcinoid, but tumour size, depth of invasion, and metastases are likely to be associated with survival rate. Once the changes in the gallbladder take place, either parietal or intralumenal, the decision of a surgical intervention must be made for a favorable prognosis. At histopathological examination of the piece, typical cells can be found, which may suggest the presence of a carcinoid. Invasion of neighbouring structures is a negative predictive factor, as opposed to a tumour limited to the level of the gallbladder walls, when the prognosis is statistically better[14,15].

Conclusions

Gallbladder carcinoid is a rare neoplasm and the diagnosis is most often made postoperatively, after anatomopathological examination. The presentation varies considerably, but most often patients report symptoms characteristic of acute or chronic cholecystitis due to gallstones.

The preoperative diagnosis of this condition is difficult, due to limited resources in terms of imaging explorations of the gallbladder. The pathology is more common in females and the elderly.

In order to improve the survival rate of patients with gallbladder neuroendocrine tumours, the appropriate treatment remains the surgical one. In this situation, this type of tumour must be considered as aggressive as gallbladder adenocarcinomas.

The role of radiotherapy and chemotherapy remains uncertain, because only a few clinical data exist. Due to the neuroendocrine component of the tumour, endocrinological monitoring is also required.

Author Contributions:

G.A. was responsible for the diagnostic procedures, clinical diagnosis and treatment decisions. M.T.A and V.F. performed the surgical intervention. G.A, M.T.A and V.F wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient included in the study" "No funding for this study"

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None

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