

Mixed Neuroendocrine Carcinoma of the Gallbladder[☆]

Carcinoma neuroendocrino mixto de vesícula

Gallbladder cancer is the most frequent neoplasm of the biliary tree. It is the fifth most common malignant tumor of the digestive tract and represents 1% of all cancers.¹ Gallbladder cancer is usually diagnosed after cholecystectomy.

Poorly differentiated neuroendocrine carcinoma, a mixed type of small and large cells, is a rare neoplasm that is classified as a carcinoid tumor.^{2,3}

We present the case of a 63-year-old patient with a history of arterial hypertension who came to our emergency department due to fever that had been developing over the previous 6 weeks and was accompanied by asthenia, anorexia and weight loss.

An abdominal computed tomography (CT) scan demonstrated an edematous and lithiasic gallbladder with focal lesions in the liver parenchyma. Antibiotic treatment was initiated (carbapenem), which improved the symptoms.

On another follow-up CT scan, the gallbladder presented similar characteristics to the initial CT and a space-occupying lesion (SOL) of the central liver was found that was hypodense

and apparently infiltrated the portal vein. Malignancy could not be ruled out.

With a diagnosis of suspected gallbladder cancer, we operated on the patient and found cholecystitis with a multi-lobe SOL in the liver, which was causing apparent portal thrombosis with varices in the hepatic hilum, occupying segments V-VI and part of IVb. Multiple biopsies were taken, which provided no conclusive intraoperative diagnosis, and a cholecystectomy was performed.

The pathology study reported that the gallbladder presented a poorly differentiated neuroendocrine carcinoma of a mixed small/large-cell type (Fig. 1) that infiltrated the gallbladder wall without surpassing it, and free surgical margins. The immunophenotype was: CKAE1-CKAE3 + NSE + chromogranin and synaptophysin + CD57 + c-myc + Ki 67 95%-97%.

Adjuvant therapy was begun with cisplatin and ectoposide,⁴ although more extensive surgery was ruled out due to the mass effect and possible vascular involvement. During the follow-up with ¹¹¹In-pentetreotide scintigraphy (Octreoscan

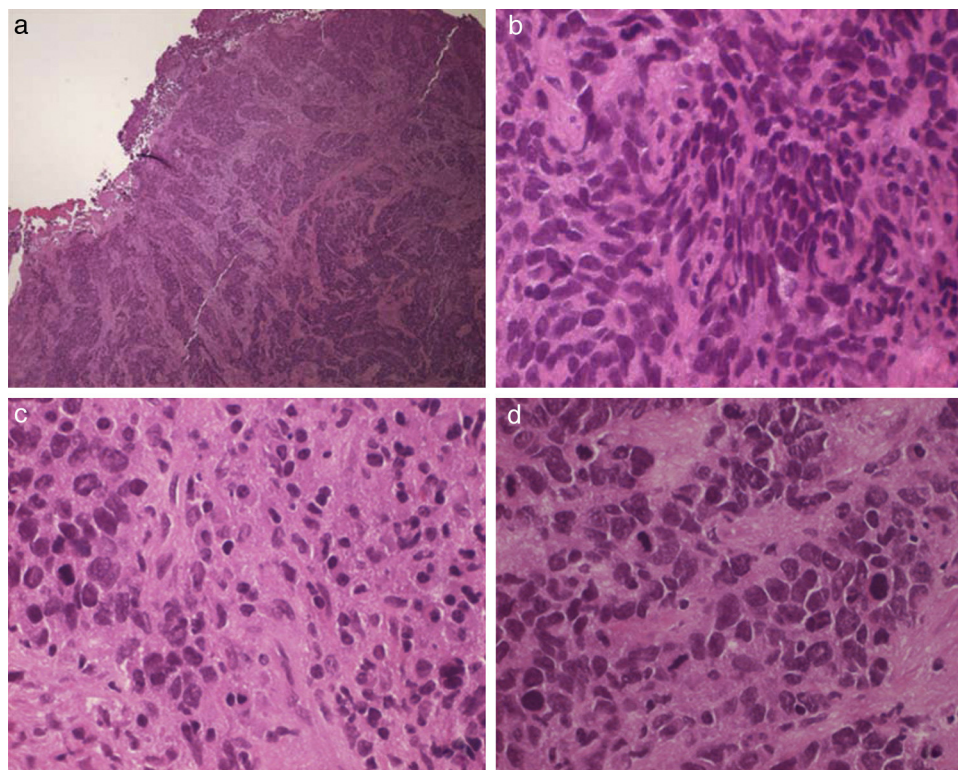


Fig. 1 – (a) General view. (b) Small cells. (c) Small and large cells. (d) Large cells and mitosis. Hematoxylin-eosin stain: (a) 4×; (b)–(d) 40×.

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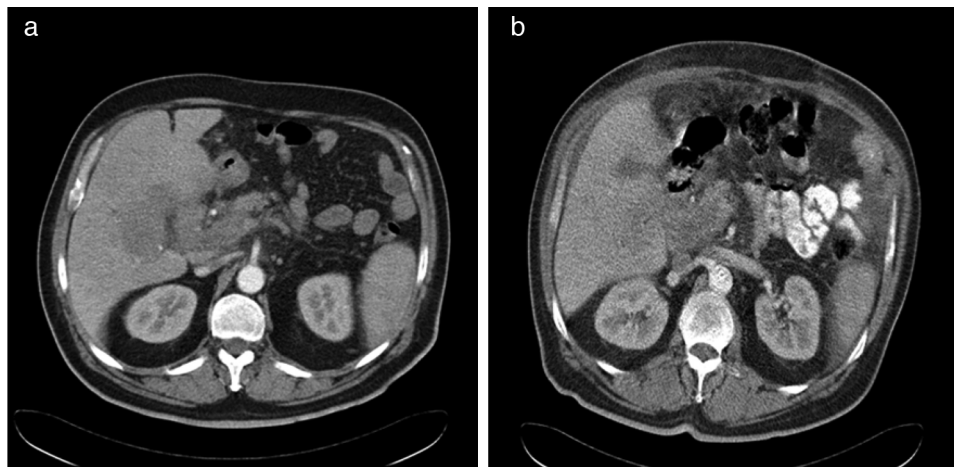


Fig. 2 – (a) Before surgery. (b) Post-surgery.

In¹¹⁾ and abdominal CT (Fig. 2), no relapse was observed after 18 months.

Reported for the first time by Albores et al. in 1984, publications of cases of this rare gallbladder neoplasm are on the rise.² A distinction is made between the small-cell type, with characteristics similar to pulmonary small-cell carcinoma, and the gallbladder carcinoid type, with differing immunohistochemical characteristics.³

The incidence of bile duct neoplasms increases with age. They predominantly affect women (4/1), with the exception of endocrine carcinomas, which are more frequent in males and at younger ages.⁵

The proposed etiology for this type of carcinoma includes cholelithiasis, obesity/diets high in carbohydrates, or porcelain gallbladder. The etiology of neuroendocrine carcinoma is not clear since the normal gallbladder mucosa does not have neuroendocrine cells.

Histologically, endocrine tumors of the extrahepatic bile ducts represent 0.2%⁵ versus 80%–90% adenocarcinomas; the most frequent forms are papillary, nodular and tubular, each with specific prognostic implications.⁶ The diagnosis of neuroendocrine carcinoma requires malignant epithelial elements (atypia, mitosis or pleomorphic nuclei).⁷ Foci of dysplasia or adenocarcinoma *in situ* can be associated with neuroendocrine cancer.⁸ The most sensitive immunohistochemical markers for small-cell carcinoma of the gallbladder are neuron-specific enolase (NSE) (75% of carcinomas), synaptophysin and chromogranin. Although less frequent, serotonin or adrenocorticotrophic hormone (ACTH) may also be present.⁵

Related symptoms can simulate biliary colic or cholecystitis, with observed jaundice, weight loss, ascites, pruritus or palpable mass. Our case presented with associated fever, weight loss, asthenia, anorexia, abdominal pain and hepatomegaly. Neuroendocrine neoplasms of the gallbladder present atypical morphological characteristics, with cholelithiasis and occasional associated endocrine manifestations and sensitivity to chemotherapy.³

Laboratory test results are non-specific. The tumor markers in our case were: prostate-specific antigen (PSA) 4.96; free PSA

0.78; carcinoembryonic antigen (CEA) 1.2; alpha-fetoprotein (AFP) 21.9; CA19-9 9.97; NSE 15.6; squamous cell antigen 0%.

While abdominal ultrasound and CT can be diagnostic for biliary tract carcinoma in general, positron emission tomography (PET-CT) and magnetic resonance cholangiopancreatography are able to determine tumor extension and stage. In biliary tract endocrine tumors, scintigraphy and endoscopic biopsies are more relevant and provide staging/follow-up and preoperative diagnosis, respectively.⁹

Diagnosis is important in order to adjust the chemotherapy regime and to consider additional treatments, such as somatostatin analogs. The differential diagnosis should include sarcomas, metastasis of melanomas and Hodgkin's lymphoma.

As for treatment, cholecystectomy is the treatment of choice for gallbladder adenocarcinoma T1a, while in stages T1b the use of simple or extended cholecystectomy is debated.¹⁰ For endocrine tumors of the biliary tract, complete resection is the standard treatment, depending on the location; those with metastatic disease or vascular involvement are usually considered unresectable, except in select cases. Extrahepatic biliary resection with hepaticojunosotomy, pancreaticoduodenectomy or cholecystectomy is the most common procedure, and liver resection or transplantation may even be required.⁹

Neuroendocrine carcinomas are silent until they metastasize or invade organs. Their diagnosis is uncommon in initial stages due to their rarity, absence of serum markers and infrequent hormonal symptoms. Pathology studies are necessary, as in our case after cholecystitis with a hepatic mass effect, which was probably inflammatory given its evolution. The prognosis is better than that of other bile tract carcinomas, especially when they are able to be resected,⁹ except if they are associated with other types.⁷

Pianna et al. reported an atypical case of neuroendocrine carcinoma that showed the combination of a small cells and club cells.⁸

In spite of their rarity, neuroendocrine carcinomas of the gallbladder should be considered a diagnostic possibility in these cases given their therapeutic and prognostic implications.

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