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Rare Mixed Adenoneuroendocrine Carcinoma of the Gallbladder: Case Report and Review of Literature

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 58-year-old
Final Diagnosis: Mixed adenoneuroendocrine carcinoma of the gallbladder
Symptoms: Abdominal pain • asthenia
Medication: —
Clinical Procedure: —
Specialty: Surgery

Objective: Rare disease

Background: Mixed adenoneuroendocrine carcinoma of the gallbladder (gMANEC) is an extremely rare cancer. Most of the cases are reported in Asia, North America, and Europe, with no cases reported in Latin America; this is the first report for this region, and the 24th case reported worldwide.

Case Report: A 68-year-old woman was referred to our department due to asthenia and moderate abdominal pain in the right upper quadrant for 6 months, with imaging examinations showing a solid heterogeneous expansive lesion in gallbladder topography and segment IV of the liver. The MRI displayed an expansive and heterogeneous lesion with inaccurate limits in the gallbladder affecting segment IVb of the liver, in addition to lymphadenopathy in the hepatic hilum. A cholecystectomy with resection of segments IV-B and V of the liver (radical cholecystectomy) and hepatic hilar lymphadenectomy were performed. Anatomopathological examination and immunohistochemistry confirmed a primary mixed adenoneuroendocrine carcinoma of the gallbladder. The patient received adjuvant chemotherapy and radiotherapy; however, after the patient reported experiencing low back pain, a CT was performed, revealing retroperitoneal metastasis, and the radiotherapy was interrupted. Currently, the patient has a stable disease, following a protocol of 5-Fluorouracil and somatostatin, and she reports having low back pain of low intensity.

Conclusions: This is the 24th gMANEC case reported in the literature. The tumor was successfully resected; however, the patient presented retroperitoneal metastasis 6 months after surgery, despite combined adjuvant therapy.

Keywords: Carcinoma • Gallbladder Neoplasms • Mixed Tumor, Malignant • Neuroendocrine Tumors

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Background

Papillary adenocarcinoma is the most common neoplasm of the gallbladder, accounting for about 98% of all cases, while critical neuroendocrine tumors account for only 0.5% of all neoplasms of this organ [1]. In 2019, the WHO classification of digestive system tumors classified the neoplasms composed of neuroendocrine and non-neuro endocrine components as mixed neuroendocrine non-neuroendocrine neoplasms (MINENs). Mixed adenoneuroendocrine carcinomas (MANEC) are an aggressive subtype of MINEN [2].

MANECs are even more difficult to diagnose as a primary tumor of the gallbladder. MANECs belong to a specific group of tumors that exhibit great heterogeneity, given that the percentages of adenocarcinomatous and neuroendocrine differentiation can vary according to their classification. To define the presence of MANEC, at least 30% of each tumor component must be determined [3]. In most cases, this tumor appears in the colon, appendix, rectum, or stomach, and is rarely found in the biliary tract, pancreas, or gallbladder [4,5].

Clinical symptoms of mixed adenoneuroendocrine carcinoma of the gallbladder (gMANEC) are nonspecific, such as epigastric or right hypochondrium pain, nausea, and vomiting [4]. However, asymptomatic cases are also reported [6-11]. These factors contribute to a late diagnosis, which worsens the prognosis and survival rates. The low number of reported cases limits the acknowledgement of primary gMANEC as a possible diagnosis.

Herein, we report a case of primary gMANEC, the first reported in Latin America and the 24th worldwide [5-22]. This case has been reported in line with the SCARE criteria [23].

Case Report

In August 2019, a 68-year-old woman was referred to the Surgical Oncology Division at the Napoleão Laureano Hospital in João Pessoa, Brazil, presenting with abdominal pain in the right upper quadrant of the abdomen and asthenia for 6 months, without associated weight loss, nausea, vomiting, or alterations in either urinary or intestinal habits. The laboratory tests showed no abnormalities. Abdominal ultrasonography (US) evidenced a solid, well-defined, hyperechogenic lesion with well-defined limits in segment IV of the liver, measuring 4.1×3.8 cm.

In our center, we perform the investigation with an abdominal computed tomography (CT), which evidenced a slightly hypodense and heterogeneous expansive lesion, measuring 4.0×3.9 cm, with heterogeneous contrast enhancement in the topography of segment IV of the liver. The referred lesion was also extending to the gallbladder site, presenting no cleavage plane with this organ. The gallbladder was partially filled with amorphous content, most likely due to a gallstone. There were no signs of dilation of intra- or extrahepatic bile ducts (**Figure 1**).

To obtain more details for a possible surgical intervention, a magnetic resonance imaging (MRI) was performed, revealing an infiltrative and heterogeneous lesion in the gallbladder, measuring approximately 8.8×5.7 cm. Moreover, the lesion presented imprecise limits and a heterogeneous signal in the T1- (**Figure 2A, 2C, 2D**) and T2-weighted (**Figure 2B**) sequences, with hypovascular contrast enhancement, affecting segment IVb of the liver. In addition, lymph node enlargement in the hepatic hilum was also detected (**Figure 2B**). To stage the neoplasm, a chest CT was performed and no alterations were evidenced. Due to the preoperative diagnosis of a gallbladder tumor, an exploratory laparotomy was indicated with a proposal for a radical cholecystectomy.

Surgical Findings and Anatomopathological Examination

During the surgery, an extensive tumor in the gallbladder was observed, extending to segments IV and V of the liver, as described in the preoperative imaging exams. Explorations of the cystic and common bile ducts were performed and no signs of neoplastic invasion were found. Lymph node enlargement was observed in the hepatic hilum; however, there were no signs of peritoneal spread or other organ metastasis. A cholecystectomy associated with resection of segments IV-B and V of the liver and lymphadenectomy of the hepatic hilum were performed. The postoperative course was uneventful and the patient was discharged on the 6th postoperative day.

The excised gallbladder and liver segments together measured 13.0×10.0×9.0 cm. The gallbladder presented a smooth and brownish external surface and greenish rough mucosa. A vegetating lesion measuring 2.0×1.0 cm was detected. Furthermore, there was a bloody area on the gallbladder surface, measuring 19.0×7.0 cm, firmly adhered to the liver.

The cuts revealed a brownish lesion, sometimes firm-elastic, sometimes friable, involving the gallbladder wall and liver parenchyma, measuring 9.0×4.0 cm. Microscopical examination showed an intestinal morphology pattern along with extensive solid areas with poorly differentiated histological grade (G3). Two of the 3 lymph nodes removed presented neoplastic invasion. There was also a perforation in the visceral peritoneal, with neoplastic infiltration in the adjacent liver segment and intratumoral coagulative necrosis. The surgical margin had no evidence of neoplastic involvement. Therefore, the pathological staging was TNM: pT3 pN1M0/IIIB.

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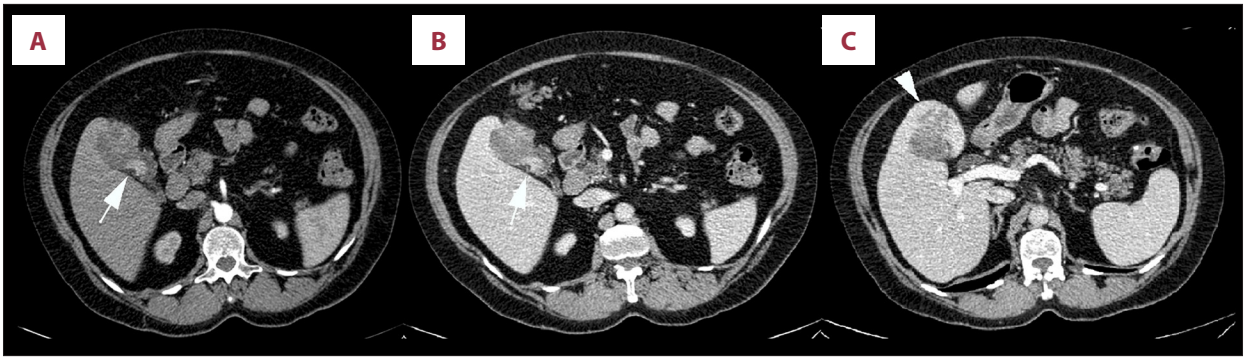

Figure 1. Preoperative CT scans: heterogenous and hypodense (head of arrow) lesion, measuring 4.0×3.9 cm, located under the projection of segment IV of the liver, without cleavage plane with the gallbladder (arrows). No signs of bile ducts dilation; **A** – arterial phase; **B** – portal phase; **C** – late phase.

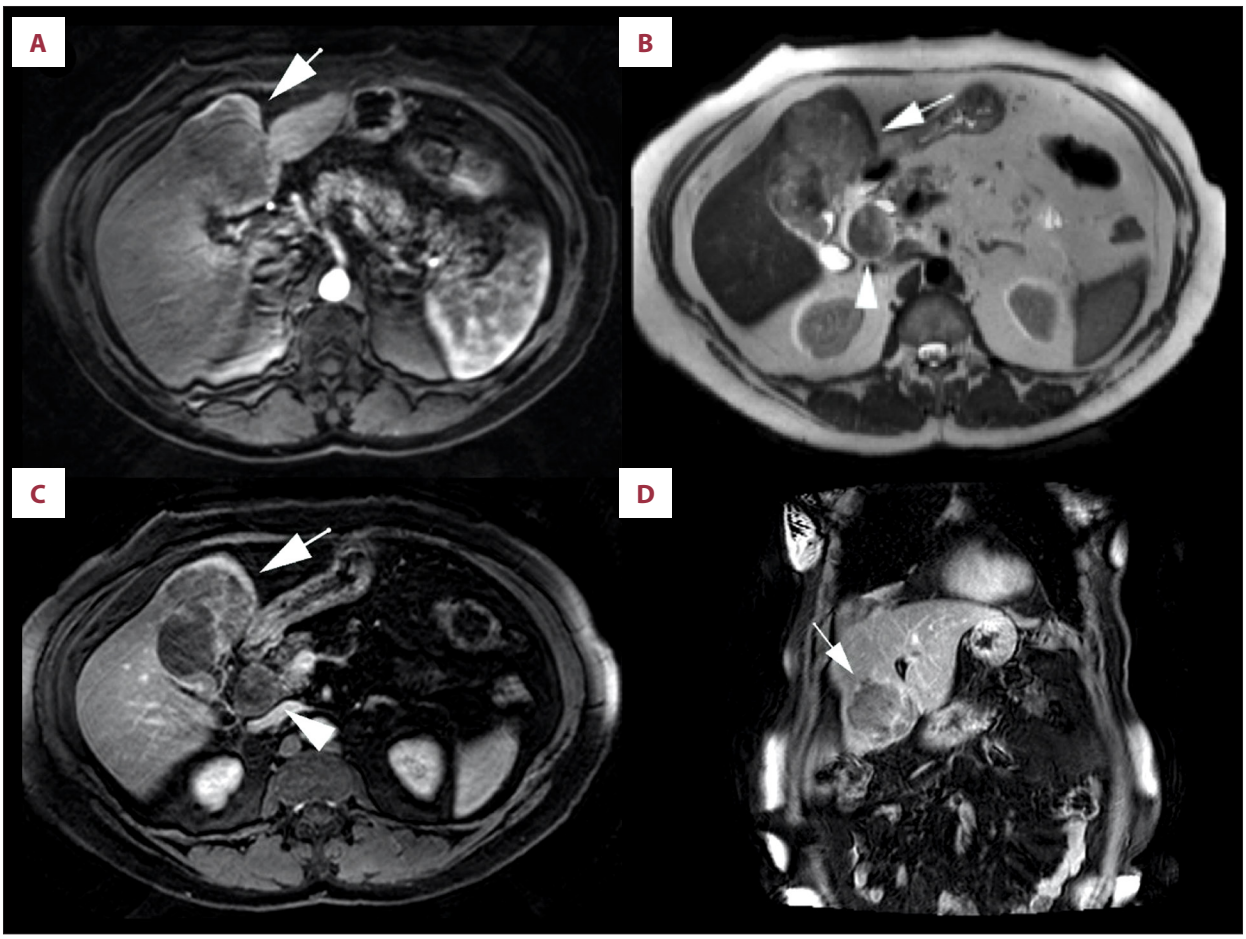

Figure 2. Preoperative MRI: expansive lesion (arrows) on the gallbladder site, with imprecise limits and heterogeneous signal in the T1- (**A, C, D**) and T2-weighted (**B**) sequences, with hypovascular contrast enhancement in all phases (arterial, portal and late phases), affecting segment IVb of the liver; and lymph node enlargement in the hepatic hilum (**B** – arrowhead).

Histopathology evidenced 2 morphological components, one with neuroendocrine differentiation and the other with poorly differentiated adenocarcinomatous component (**Figure 3A**). The immunohistochemical (IHC) study of the tumor cells was positive for the following markers: CK7 (SP52), CK20 (SP33) in foci, Synaptophysin (SynA), and chromogranin A (CgA), CDX2 (AMT 28), and the proliferation index Ki-67 was 90% (**Figure 3B**). Therefore, a mixed adenoneuroendocrine carcinoma of the gallbladder (gMANEC) was confirmed.

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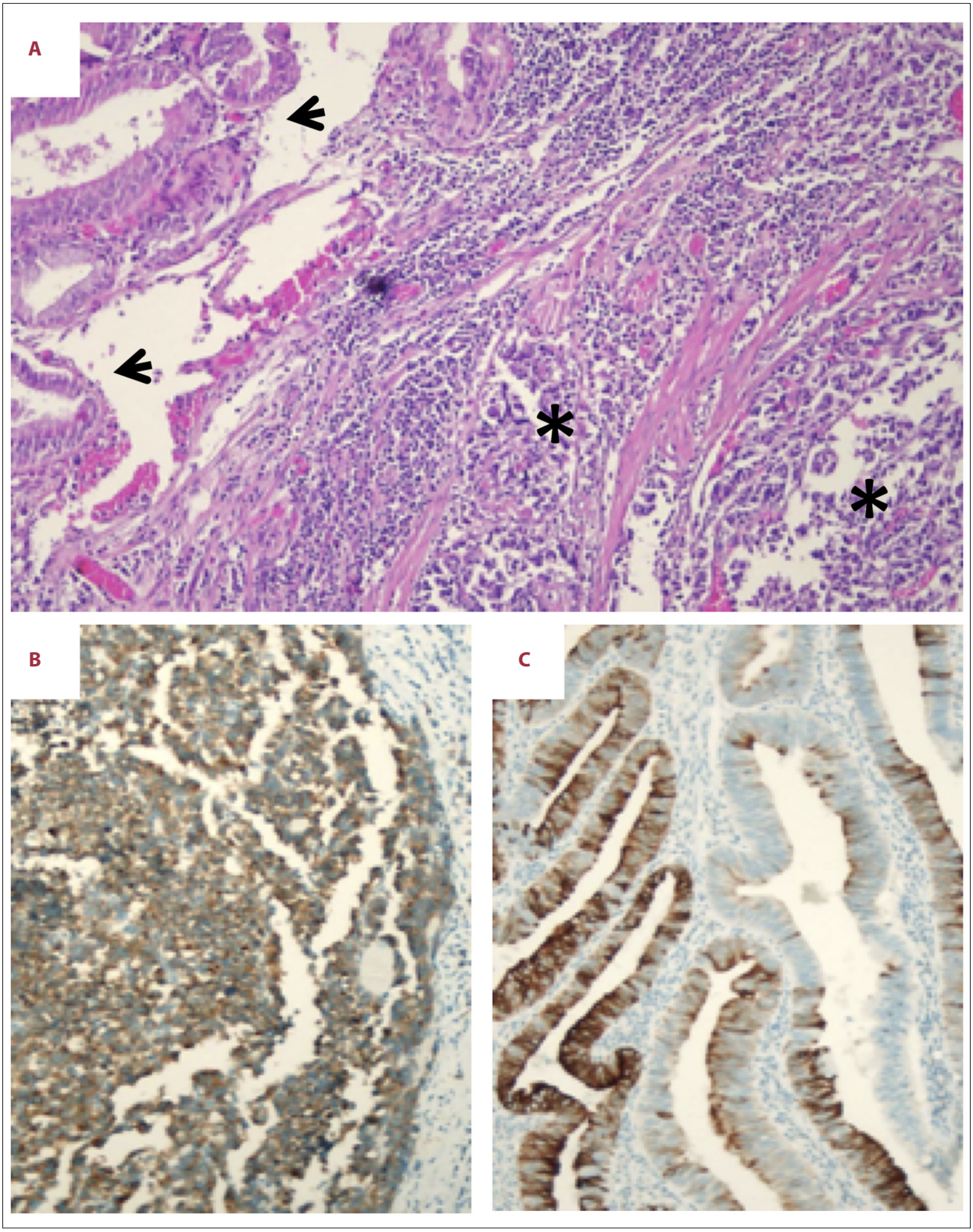

Figure 3. Mixed adenoneuroendocrine carcinoma of the gallbladder stained with Hematoxylin and Eosin (H&E): adenocarcinomatous (arrow) and neuroendocrine (*) components (**A**); immunohistochemical (IHC) staining for CgA in the neuroendocrine portion (**B**) and CK7 (SP52) in the adenocarcinomatous portion (**C**).

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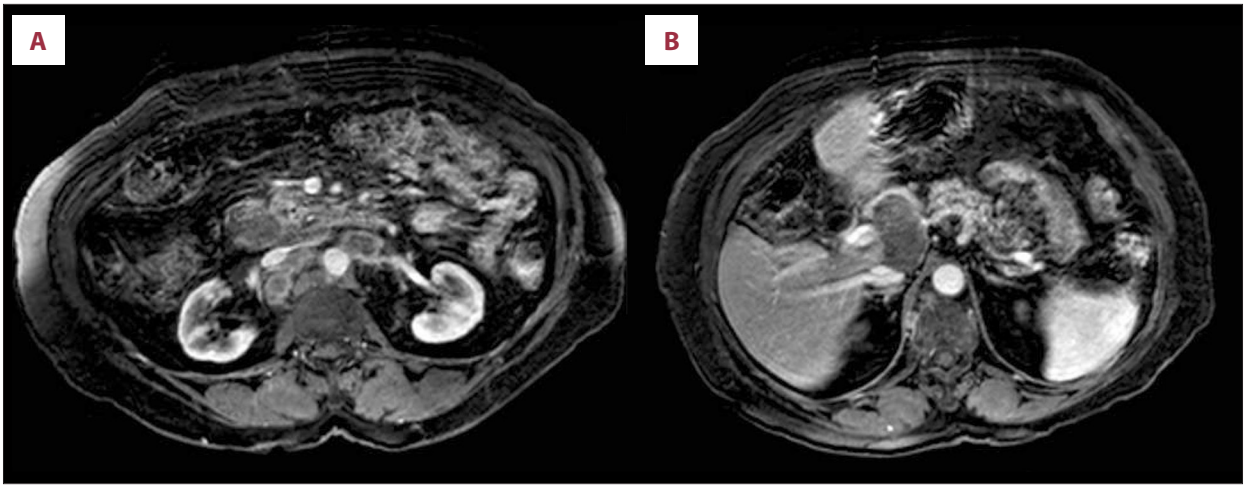

Figure 4. Postoperative MRI showing multiple retroperitoneal lymph nodes enlargements in para-aortic and precaval situation (**A**) and around the celiac trunk and hepatic artery (**B**).

Postoperative Course

The patient has been followed up by clinical oncology with the initial proposal of adjuvant treatment with 10 chemotherapy sessions with 5-Fluorouracil (5-FU) and radiotherapy. Initially, the oncology team opted not to prescribe somatostatin analogs due to the absence of symptoms related to neuroendocrine neoplasm. However, 6 months after surgery, the patient started reporting persistent low back pain of moderate intensity. A CT was then performed, revealing retroperitoneal metastasis, evidenced by multiple lymph nodes enlargement in para-aortic, retrocaval, and precaval locations at the level of the pancreas head (**Figure 4A, 4B**). Therefore, radiotherapy was interrupted and somatostatin analogs were started. Currently, 3 months later, the patient has stable disease, with mild back pain.

Discussion

The majority of the literature on gMANEC consists of case reports and small case series, all from Asia (67%), North America, and Europe. Moreover, to date, only 23 cases had been described, and none were from Latin America (**Table 1**). To date, including data from the present study, the mean age of patients with gMANEC is 61 years and the sex ratio is 5: 19 (male: female).

As mentioned above, the clinical features of gMANEC are nonspecific [4]. A recent systematic review, published in 2019, showed that the majority of them (60%) presented epigastric or right upper quadrant (RUQ) pain, whereas 40% were asymptomatic at diagnosis [4]. Furthermore, MANECs can be classified as functional or non-functional depending on the hormone synthesis and endocrine syndrome inductions, although only 3.3% presented syndromes involving hormone production [1] and most of the patients do not present carcinoid syndrome [24].

Besides these nonspecific clinical features, imaging examinations also show low accuracy in this diagnostic process, which highlights the importance of the postoperative histopathological examination in confirming the diagnosis [19]. Moreover, frequently, only a single histological component of the tumor is identified, which impairs the diagnosis and treatment processes [6]. Therefore, chromogranin A (CgA) and synaptophysin (SynA) markers are of paramount importance, given their high sensitivity for MANECs diagnosis, being present in up to 92.3% of patients [4].

The World Health Organization (WHO) Grading for Neuroendocrine Tumor establishes 3 degrees of tumor differentiation: G1 (mitotic count <2 per 10 HPF and/or a Ki-67 index ≤2%); G2 (mitotic count 2-20 per 10 HPF and/or Ki-67 index of 3-20%); and G3 (mitotic count >20 per 10 HPF and/or Ki-67 index >20%) [3]. NETs classified as G1 or G2 are associated with a better prognosis than the NETs of other histological subtypes [25]. In our case, the neuroendocrine portion presented a Ki-67 index of 90%, which would make it a neuroendocrine neoplasm of third grade or low differentiation according to the WHO classification [6,25,26]. Moreover, the adenocarcinoma portion was also classified as Grade 3; therefore, a poor prognosis is expected.

The ideal therapy is still undetermined, although the combination of complete surgical resection, adjuvant chemotherapy, and the use of somatostatin seems to be the mainstay of treatment [4]. In the majority of cases reported in the literature, the decision was made to perform a radical cholecystectomy, with segmentectomy (segments IV and V) of the liver along with lymphadenectomy. Generally, it is expected that 74% of

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Table 1. Previous reported cases of mixed adenoneuroendocrine carcinoma of the gallbladder.

Author	Age	Sex	Primary symptoms	Stage	CgA	SynA	Treatment	Outcomes
Our case	68	F	RUQ pain	IIIb	+	+	RC+Radiotherapy+5-FU	Retroperitoneal metastasis 6 months after surgery
Yannakou, 2001 [7]	72	F	Epigastric pain, nausea, weight loss	N/A	–	–	RC	Died 2 months after the surgery
Shimizu, 2006 [1]	58	M	Epigastric pain	IVa	+	N/A	Right hepatic trisegmentectomy	Tumor recurrence 3 months after surgery. Died 4 months after surgery
Oshiro, 2008 [8]	55	F	Back pain, fever, epigastric pain	IIIa	+	+	Pancreaticoduodenectomy, gallbladder, bile duct, and liver	Alive without signs of recurrence 20 months after surgery
Sato, 2010 [16]	68	F	Asymptomatic	N/A	+	+	RC, 4 and 5 liver segmentectomy	Alive without signs of recurrence 12 months after surgery
Mondolfi, 2011 [18]	48	F	RUQ pain	N/A	+	+	Extended left lobectomy, partial right hepatectomy	Surgery was successful and the patient recovered without complications
Song, 2012 [24]	55	F	Epigastric pain	IIIa	+	+	RC and lymph node dissection in hepatoduodenal ligament and common hepatic artery+SST+NACT: Carboplatin, VP16, Paclitaxel+Octreotide	Alive without signs of recurrence 7 months after surgery
Abe, 2013 [14]	81	F	Asymptomatic	N/A	+	+	RC	Alive without signs of recurrence 4 years after surgery
Shintaku, 2013 [9]	80	M	Asymptomatic	N/A	+	+	RC	Alive without signs of recurrence 8 months after surgery
Chatterjee, 2014 [17]	73	F	Asymptomatic	I	+	+	RC+External beam radiotherapy with 5-FU	11 months after surgery, a metastatic nodule on the anterior abdominal wall was detected
Chen, 2014 [10]	34	M	RUQ pain	N/A	+	+	RC and radical lymph node dissection (adjuvant chemotherapy was refused)	Alive with lymph node enlargement in the retroperitoneum and hepatic hilum at 4 months after surgery
Meguro, 2014 [15]	54	F	Epigastric pain	II	+	+	RC, Extrahepatic bile duct resection, lymph node dissection, and hepaticojejunostomy	Alive without signs of recurrence 24 months after surgery
Acosta, 2015 [12]	55	F	Epigastric and RUQ pain	N/A	+	+	Robotic-assisted LC and Revision surgery	A second surgery was scheduled to complete an oncologically adequate procedure
Azad, 2015 [11]	62	F	Asymptomatic	N/A	N/A	+	RC	Alive and asymptomatic 2 years after surgery

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Table 1 continued. Previous reported cases of mixed adenoneuroendocrine carcinoma of the gallbladder.

Author	Age	Sex	Primary symptoms	Stage	CgA	SynA	Treatment	Outcomes
Kanetkar, 2018 [19]	77	F	N/A	IIIb	N/A	N/A	RC+NACT: 3 cycles of carboplatin-etoposide	6 months follow-up after surgery. 6 months without signs of recurrence
	63	F	Asymptomatic	II	N/A	N/A	Revision RC+ACT: 6 cycles of carboplatin-etoposide	3 months follow-up after surgery. 3 months without signs of recurrence
	50	M	N/A	II	N/A	N/A	Revision RC+ACT: 6 cycles of carboplatin-etoposide	3 months follow-up after surgery. 3 months without signs of recurrence
	47	F	N/A	IIIa	N/A	N/A	RC	22 months follow-up after surgery. 22 months without signs of recurrence
	64	F	N/A	IIIb	N/A	N/A	RC	7 months follow-up after surgery. 4 months without signs of recurrence
Lin, 2018 [20]	43	F	RUQ pain	IIIa	+	+	RC, partial liver resection, radical lymph node dissection+SST+ACT: 6 cycles of cisplatin+etoposide +octreotide	Alive 21 months after surgery
Parsa, 2018 [5]	74	F	Epigastric and abdominal pain	N/A	+	_	Laparoscopic cholecystectomy with a wedge resection of the liver	N/A
	76	M	RUQ pain, fever, jaundice	N/A	+	+	Open cholecystectomy	N/A
Sciarra, 2019 [21]	66	F	Abdominal pain	N/A	+	+	RC+hepatic resection of the vesicular bed+retro-duodenal lymph nodes resection+lymph nodes close to hepatic artery resection	Alive and asymptomatic 5 months after surgery
Kamei, 2020 [22]	53	F	N/A	IVb	–	+	Extended left hemihepatectomy with extrahepatic bile duct resection+NACT: gemcitabine and cisplatin for 12 months	6 months after surgery, metastatic disease in the Morrison's pouch was discovered. Died 27 months after the surgery

CgA – chromogranin A; SynA – synaptophysin A; F – Female; M – Male; RC – radical cholecystectomy; RUQ – right upper quadrant; N/A – not available; 5-FU – 5-Fluorouracil; SST – somatostatin; NACT – neoadjuvant chemotherapy; ACT – adjuvant chemotherapy.

patients undergoing cholecystectomy due to a gallbladder neuroendocrine tumor will present recurrence or metastasis; however, a cholecystectomy combined with hepatic segmentectomy and lymphadenectomy increases the 5-year survival rate from 21.3% to 60.4% in patients with this type of tumor [24].

Evidence suggests that neoadjuvant chemotherapy has good results, but it remains restricted to the few cases of MANEC diagnosed preoperatively [4,14]. However, due to the tumor's rarity and histological heterogeneity, there are no established adjuvant chemotherapy protocols for gMANEC, which makes it difficult to determine its effectiveness [4,27,28]. Therefore, the adjuvant therapy usually targets the most aggressive component of the tumor [5,6,29].

The prognosis depends on the size of the tumor, infiltration, differentiation, and metastasis [24,30]. The unpredictable biological behavior of MANECs contributes to an uncertain prognosis that seems to be poor [5]. There is evidence that the neuroendocrine component of the tumor may present a higher proliferative rate than the adenocarcinomatous, suggesting that this component may influence the long-term results in these

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patients [1]. However, there are too few cases of MANEC to form definitive conclusions regarding how it acts.

The main limitation of this report is the short follow-up of the patient, which prevented determination of the long-term prognosis. However, even with this short-term follow-up, the patient had already presented recurrence, with metastatic disease to the retroperitoneum, revealing a poor prognosis.

Conclusions

Our case is the first Western study to report metastasis in the first 6 months after surgical resection. In addition, the unpredictable biological behavior of gMANEC was also observed, since even after successful surgery and adjuvant therapy, early recurrence of disease was detected. Thus, it demonstrates the importance of careful follow-up by the medical team and the need to standardize more effective adjuvant therapy protocols and follow-up guidelines. Current recommendations do not assist in medical team decision-making, since early disease recurrence is also reported in the post-surgical period of low-stage gMANEC. More studies are needed regarding this neoplasm, especially ones focused on improving the patient's prognosis.

Primary gMANEC is still a challenging pathology with a low number of cases reported in the literature. Our case presents an early recurrence of disease, demonstrating the importance of careful follow-up by the medical team. More studies are needed regarding this neoplasm, especially research focused on improving the patient's prognosis.

Ethics Approval

This study was approved by the Ethics Committee of our Institution under the registration number CAAE: 27616620.4.0000.8807.

Conflict of Interests

None.

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