

CASE REPORT

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Hepatobiliary neuroendocrine carcinoma: a case report

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Abstract

Introduction: Neuroendocrine carcinoma of the gallbladder is a rather uncommon disease. We report a case of a neuroendocrine tumor that was located in the wall of the gallbladder and that extended into the liver.

Case presentation: A 52-year-old Caucasian woman presented with right-sided abdominal pain, ascites and jaundice. An MRI scan revealed a tumor mass located in the gallbladder wall and involving the liver. A partial hepatectomy and cholecystectomy were performed. Histology revealed a neuroendocrine tumor, which showed scattered Grimelius positive cells and immuno-expressed epithelial and endocrine markers. Our patient is undergoing chemotherapy treatment.

Conclusion: Gastroenteropancreatic neuroendocrine tumors need a multidisciplinary approach, involving immunohistochemistry and molecular-genetic techniques.

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) constitute a heterogeneous group of neoplasms. Two major GEP-NET subcategories are intestinal endocrine tumors or carcinoids and pancreatic neuroendocrine tumors (PNETs).

Requests for standardization in the management of patients with gastroenteropancreatic NETs recently resulted in the development of several guidelines, including those proposed by ENETS. The TNM staging system and the grading system are based on the current WHO classifications of endocrine and digestive tumors [1-4].

The classification of GEP-NETs is based on cell morphology and the mitotic index, with well-differentiated tumors displaying monomorphic appearances and rare mitoses (<2/10 HPF), moderately-differentiated tumors displaying an intermediate morphology and mitotic rate (2-10/10 HPF) and poorly differentiated tumors consisting of pleomorphic cells with a high mitotic index (>10/10 HPF). These three histology categories of GEP-NETs (well, moderately and poorly differentiated) strongly correlates with our patient's survival. Other features of neuroendocrine tumors (such as secretion of hormones and expression of

somatostatin receptors) also correlate with histological classification. "Moderately-differentiated" neuroendocrine tumors should be recognized as a subset of GEP-NETs with a prognosis that is distinct from well- and poorly-differentiated tumors [5].

Most endocrine tumors are well differentiated and slow-growing. A few are poorly differentiated small-cell endocrine tumors that are rapidly growing and have a poor prognosis [6].

Even though the growth of GEP-NETs is slow in comparison with adenocarcinomas, it is generally recognized that, with the exception of 90% of insulinomas, almost all of them have long-term malignant potential. Most are malignant at the time of diagnosis, with 60% or more presenting with metastasis to the liver. The most common cause of the death is hepatic failure and malignant proliferation.

An active approach to treatment may improve our patient's quality and length of life [7].

Management strategies include surgery for cure or palliation, and a variety of other cytoreductive techniques and medical treatment, including chemotherapy and biotherapy to control symptoms due to hormone release and tumor growth, with somatostatin analogues (SSAs) and alpha-interferon. New biological agents and somatostatin-tagged radionuclides are under investigation [8].

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Gallbladder neuroendocrine tumors can cause recurrent upper quadrant pain, while extrahepatic bile duct carcinoids typically produce the sudden onset of biliary colic and painless jaundice and ascites [9]. The histopathology of these tumors may reveal: carcinoids (well-differentiated endocrine tumors); small cell carcinomas (poorly differentiated endocrine carcinomas); and mixed endocrine-exocrine carcinomas [10]. Carcinoid tumors larger than 2 cm often extend into the liver and metastasize. The prognosis of small-cell carcinomas of the gallbladder is poor [11].

Case presentation

A 52 year-old Caucasian woman presented with right-sided abdominal pain (upper quadrant pain), ascites and jaundice. She had been experiencing the abdominal pain for one year.

An MRI revealed a tumor mass located in the liver, extrahepatic bile ducts and gallbladder. Tests done at the time of admission revealed raised levels of serum amylase (490-600 IU/L), abnormal liver function (Gamma-glutamyl transpeptidase 372 IU/L; Alkaline phosphatase 1309 IU/L) and a total bilirubin of 1.90 mg/dl. With a clinical diagnosis of obstructive jaundice, our patient underwent imaging studies. The primary clinical diagnosis was liver tumor. A partial hepatectomy and cholecystectomy were performed.

Part of the liver measured 16 × 13 × 8 cm and the gallbladder 9.5 × 3.5 cm. The tumor was located in the wall of the gallbladder infiltrating the liver. The nodular mass measured 6 cm at its greatest axis, was found in

the wall of the gallbladder involving the liver, and was a grey-white to yellow color. Thirteen lymph nodes diameters of 0.3 cm to 1 cm were found.

Specimens were fixed in 10% neutral buffered formalin, and paraffin embedded sections were prepared. The sections were processed for conventional histopathological examination as well as for immunohistochemistry using a standard avidin-biotin-peroxidase complex technique. Negative and positive controls were included for each batch of slides tested.

The tumor was composed of round to fusiform cells with round to ovoid hyperchromatic nuclei, arranged in sheets, nests, cords, and festoons. There were rosette-like structures and tubules present, extensive necrosis, as well as basophilic staining of the vessels. Mitotic figures were frequent.

Carcinoma cells were Grimelius positive. In addition, tumor cells immunoexpressed epithelial markers such as CK, CK7, CK19 +/-, and endocrine markers such as NSE (1+), chromogranin A (1+); while C-KIT was negative, ER negative, PR negative, Alfa fetoprotein negative, CEA negative, Ki67 positive (low <5%), Vimentin negative and synaptophysin negative.

The histopathological diagnosis was a GEP-NET tumor. Our patient is undergoing targeted therapy, including: Gleevec (Novartis) (Figure 1, Figure 2, Figure 3, Figure 4, Figure 5, Figure 6, Figure 7, Figure 8).

Discussion

Hepatic neuroendocrine carcinoma is extremely rare and was first described in 1958 [12]. As of 2001, only 53

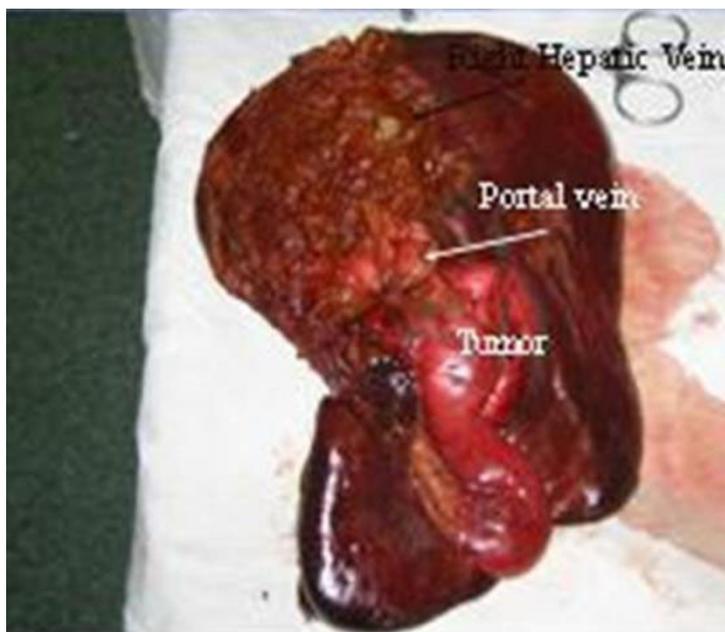


Figure 1 Gross examination of the liver and gallbladder.

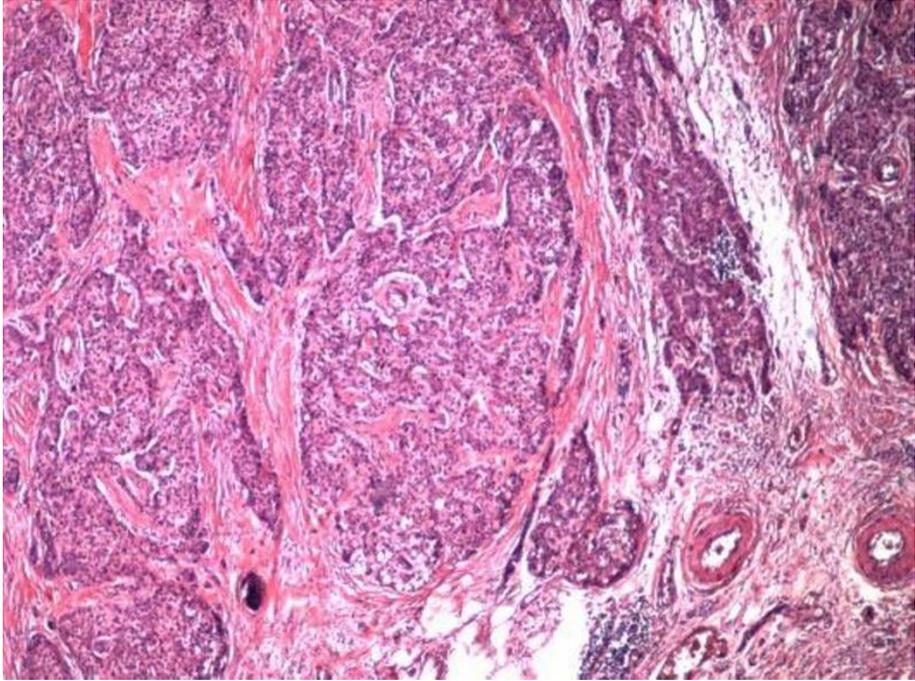


Figure 2 Tumor cells invading the wall of the gallbladder Hematoxylin and eosin 5x.

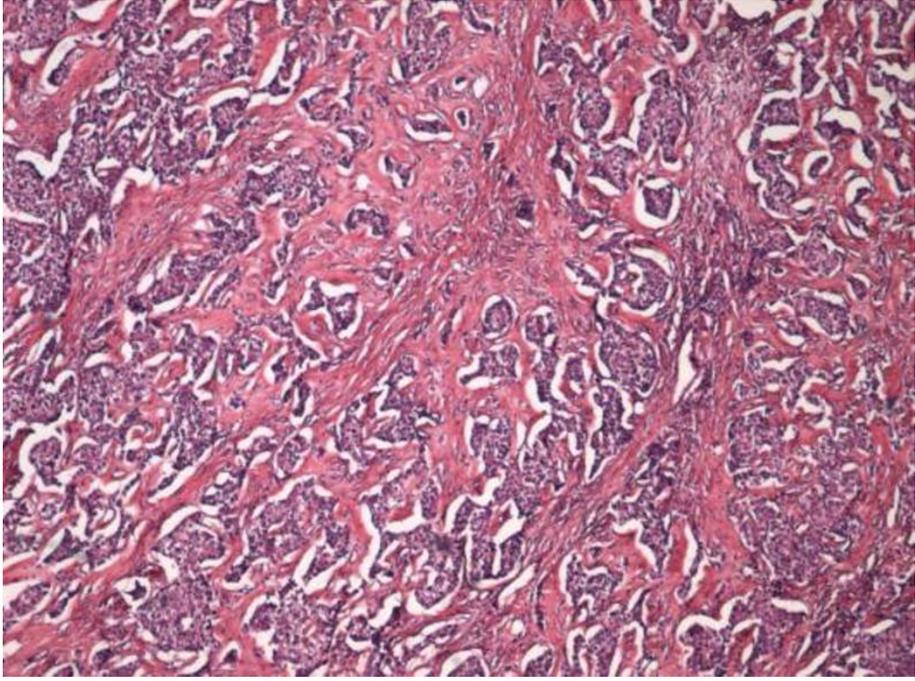


Figure 3 Paraffin embedded tissue, histological examination (hematoxylin and eosin 5x).

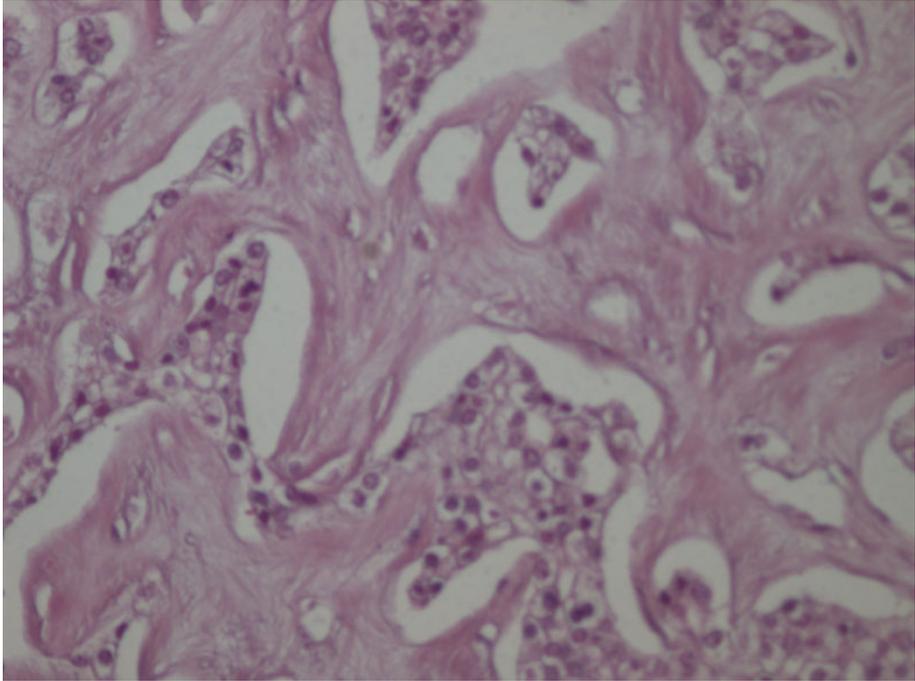


Figure 4 Paraffin embedded tissue, histological examination (hematoxylin and eosin 20×).

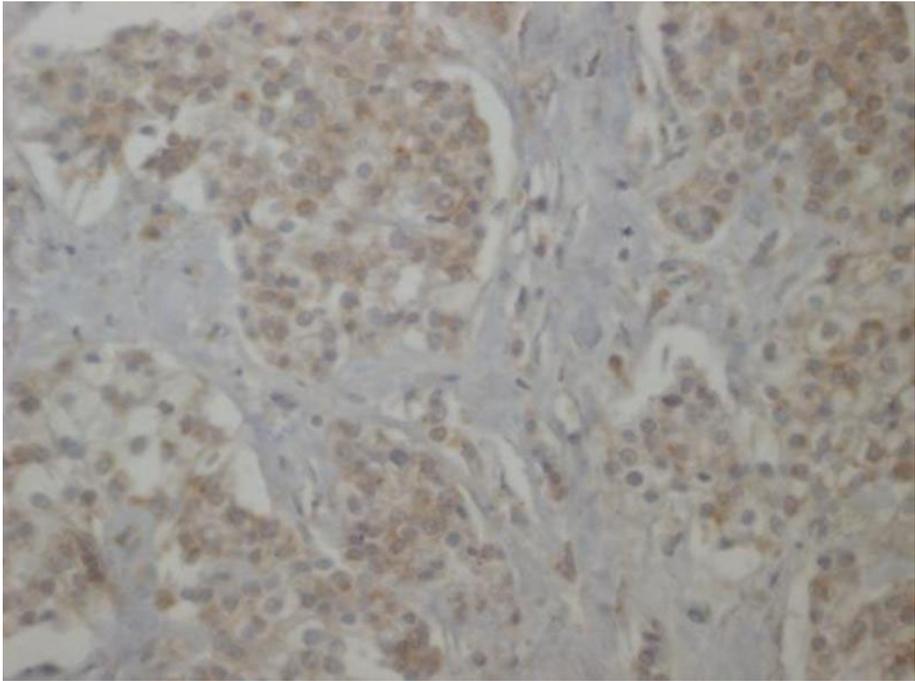


Figure 5 Paraffin embedded tissue, Immunohistochemical examination, Cg A (10×).

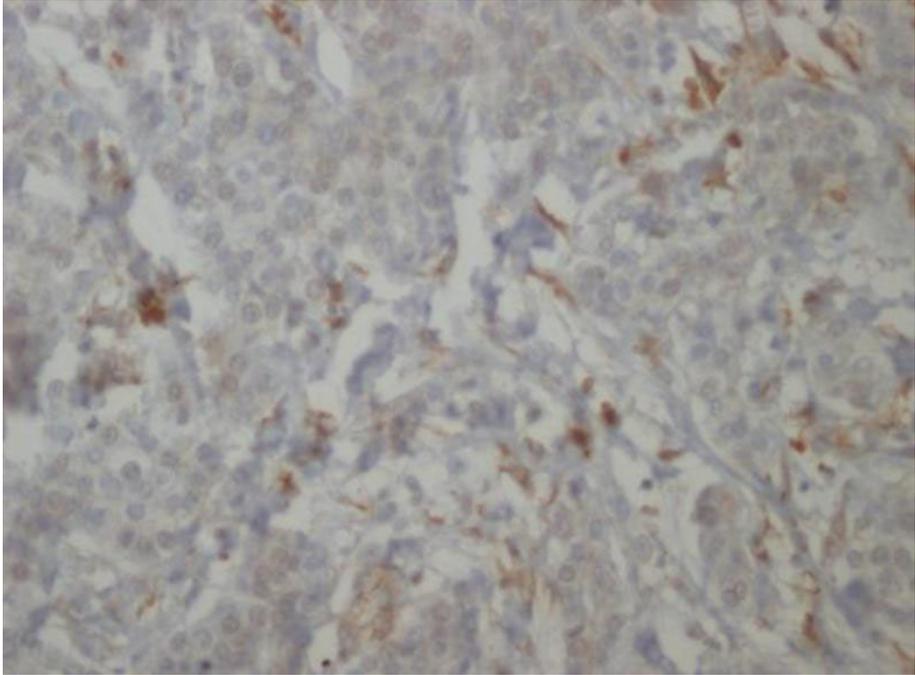


Figure 6 Paraffin embedded tissue, Immunohistochemical examination, NSE (20×).

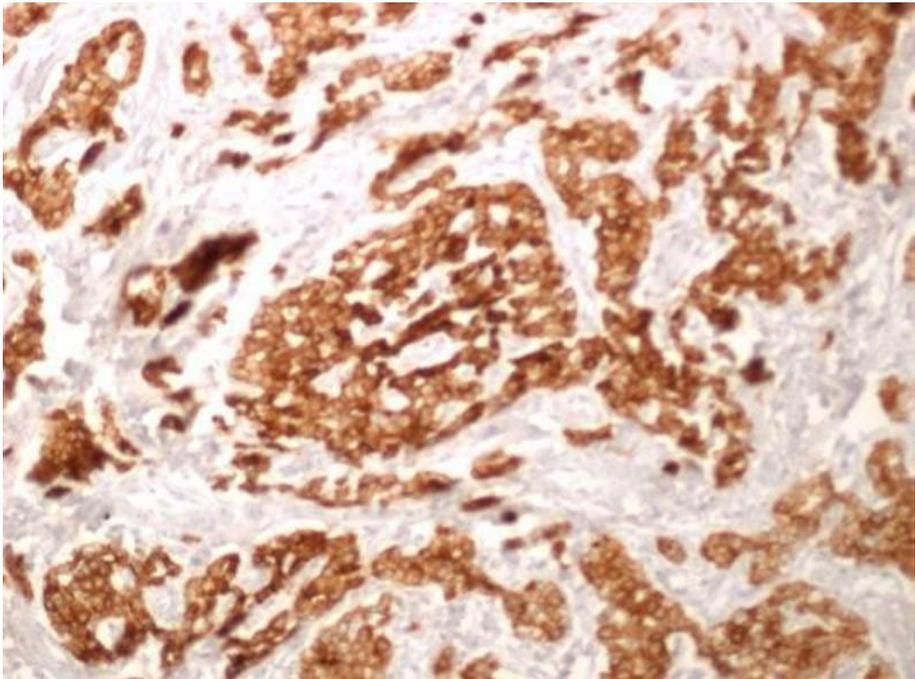


Figure 7 Immunohistochemical examination, CK (20×).

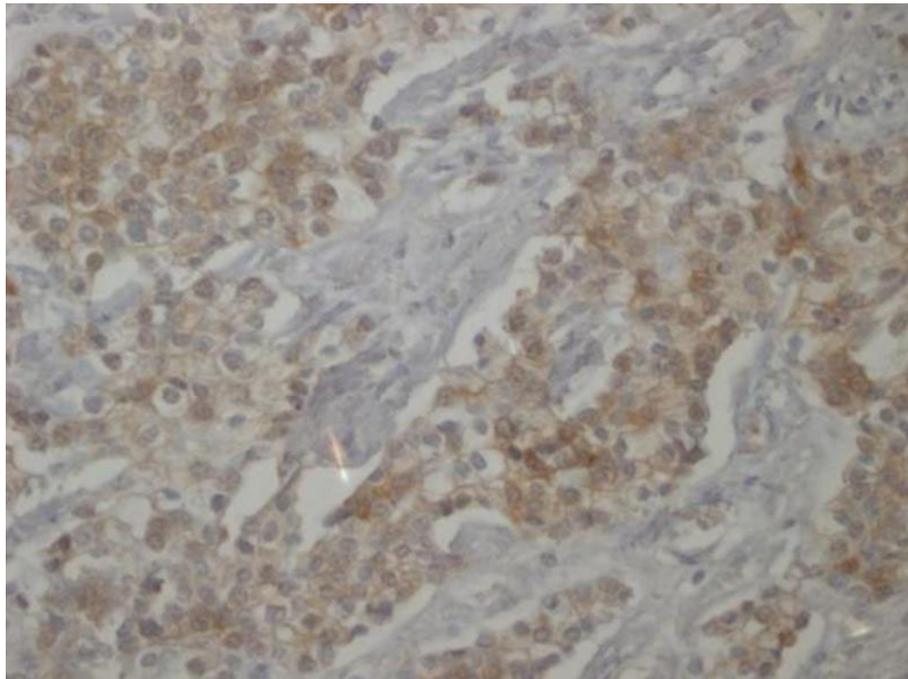


Figure 8 Immunohistochemical examination, CK 19 (20×).

cases have been reported in English literature [9]. These tumors were mostly found in middle-age patients and were more frequently in women.

Neuroendocrine carcinoma of the gallbladder is uncommon in humans. Only 4% of epithelial tumors of the gallbladder are neuroendocrine carcinoma, which is reported to have a poor prognosis [13,14].

Bile duct and gallbladder neuroendocrine carcinomas arise from pre-existing neuroendocrine cells in the epithelium. Molecular genetic techniques will probably aid in a more clear-cut picture of the molecular background of oncogenesis and the progression of these tumors [15].

GEP-NET tumors should be treated with a multidisciplinary approach, including a partial hepatectomy, prophylactic cholecystectomy, and an excision of the lymph nodes and the primary tumor [16-19].

Receptor radionuclide therapy is a promising treatment modality for patients with neuroendocrine tumors and for whom alternative treatments are limited [20].

Since 2000, patients with somatostatin receptor-positive metastatic, inoperable GEP-NETs and malignant pheochromocytomas have been treated with the radiolabeled somatostatin analogue [$^{177}\text{Lu-DOTA}^0$, Tyr 3] octreotate (^{177}Lu -octreotate). Results 177 of Lu-octreotate treatment in these patients are promising, with a tumor size reduction in 47% of the treated patients [21].

Conclusion

Gastroenteropancreatic neuroendocrine tumors need a multidisciplinary approach, involving immunohistochemistry and molecular-genetic techniques.

Consent

Written informed consent was obtained from our patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations

CgA: chromogranin; CK: cytokeratin; ENETS: European Neuroendocrine Tumor Society; GEP-NETs: gastroenteropancreatic neuroendocrine tumors; NSE: neuron specific enolase; PNETs: pancreatic neuroendocrine tumors; TMN: tumor-node-metastasis

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Authors' contributions

All authors were all involved in the conception of the case report, data collection, review of literature and writing the manuscript. SMK performed the histological examination of the gallbladder and liver and was a major contributor in writing the manuscript. GP performed the immunohistochemical examination and interpretation. HM and VSM analyzed and interpreted the clinical data. SL performed the data collection. NL performed the surgery. LSH reviewed the literature. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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