Neuroendocrine tumor of the cystic duct

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Abstract

Neuroendocrine tumours of the extrahepatic bile ducts are extremely rare with less than 70 cases having been reported in the literature. Neuroendocrine tumours are neoplasms of variable malignant potential that arise from the embryonic neural crest cells. They most commonly occur in young females and usually present with painless jaundice. Preoperative diagnosis is seldom made and neuroendocrine tumours are usually incidentally found during abdominal surgical intervention for other indication. Due to their indolent biological behaviour aggressive surgical treatment is recommended. We present a case of an incidentally discovered neuroendocrine tumour of the cystic duct in a 41 year old woman following laparoscopic cholecystectomy for symptomatic gallbladder microlithiasis. The present case is the 8th case of cystic duct NET and the 63rd of extrahepatic bile duct NET. While a rare location for a NET, it is important to report cases of biliary tract neuroendocrine tumours in order for their pathogenesis and physical history to be clarified. (Acta gastroenterol. belg., **2012**, 75, **357-360**).

Keywords : carcinoid, chromogranin, extrahepatic bile ducts.

Introduction

Neuroendocrine tumors (NETs) are neoplasms of variable malignant potential that arise from the embryonal neural crest cells, also called enterochromaffin or argentaffin or Kulchitsky cells, that, during development, migrate to the gastrointestinal and respiratory system and that express general markers of neuroendocrine differentiation and hormones (1,2,3). NETs are rare tumors, with an incidence ranging from 0,001 to 0.65% (4), which usually occur in the gastrointestinal (67.5%) and respiratory tract (25.3%) (5). Within the gastrointestinal tract they are mainly found in the vermiform appendix (45%), the ileum (28%) and rectum (16%) (2). NETs of the biliary tree are extremely rare and account for 0.2-2% of all gastrointestinal NETs, a fact explained by the paucity of enterochromaffin cells in the extrahepatic bile ducts (3). Chronic inflammation of the bile ducts leads to intestinal metaplasia of the mucosa and increased number of enterochromaffin cells (6). Only 62 cases of biliary tract NETs have been reported, from which only 7 occurred in the cystic duct (6). We present a case of a small NET of the cystic duct, which was discovered postoperatively after histopathological analysis of the gallbladder resected during routine laparascopic cholecystectomy for microcholelithiasis.

Case report

A 41 year old female was admitted to our hospital for routine laparoscopic cholecystectomy. The patient had an episode of biliary colic two months ago. The gallbladder echo revealed microlithiasis. Also, the patient had type B Wolf-Parkinson White syndrome. Laparoscopic cholecystectomy was performed without any complications and the patient's postoperative course was uneventful.

The resected specimen consisted of the gallbladder, the cystic duct and the cystic duct lymph node. Histopathologic examination of the specimen revealed the presence of a NET of the cystic duct. Specifically, about 5 mm from the surgical margin, a neoplasm was observed in the lamina propria of the bile duct, not extending through the muscular layer, measuring 1 × 3 × 2 mm. The tumor consisted from small and rarely medium size cells, in an organoid pattern, with round relatively uniform nuclei with dense chromatin (Fig. 1). Atypia, necrosis or increased mitotic activity was not observed. Immunohistochemistry revealed intense positivity to synaptophysin, chromogranin, and NSE and only mild positivity to CD 56 and CAM 5.2 (CK8/18), while the tumor cells were negative for keratins CK 7 and CK 19. Ki-67 was 1-2% (Fig. 2).

Following the diagnosis, the patient has been submitted to abdominal CT and octreotide scintigraphy which didn't show any signs of residual or metastatic disease. Due to the small size of the tumor, the negative surgical margins and the absence of metastases, the patient didn't receive any adjuvant chemotherapy or radiotherapy. The patient remains asymptomatic and free of tumor metastases and recurrence fourteen months after surgery.

Discussion

Carcinomas of the bile ducts represent less than 2% of all cancers (3). Cholangiocarinoma is the most common tumor of the bile ducts accounting for up to 80% of all

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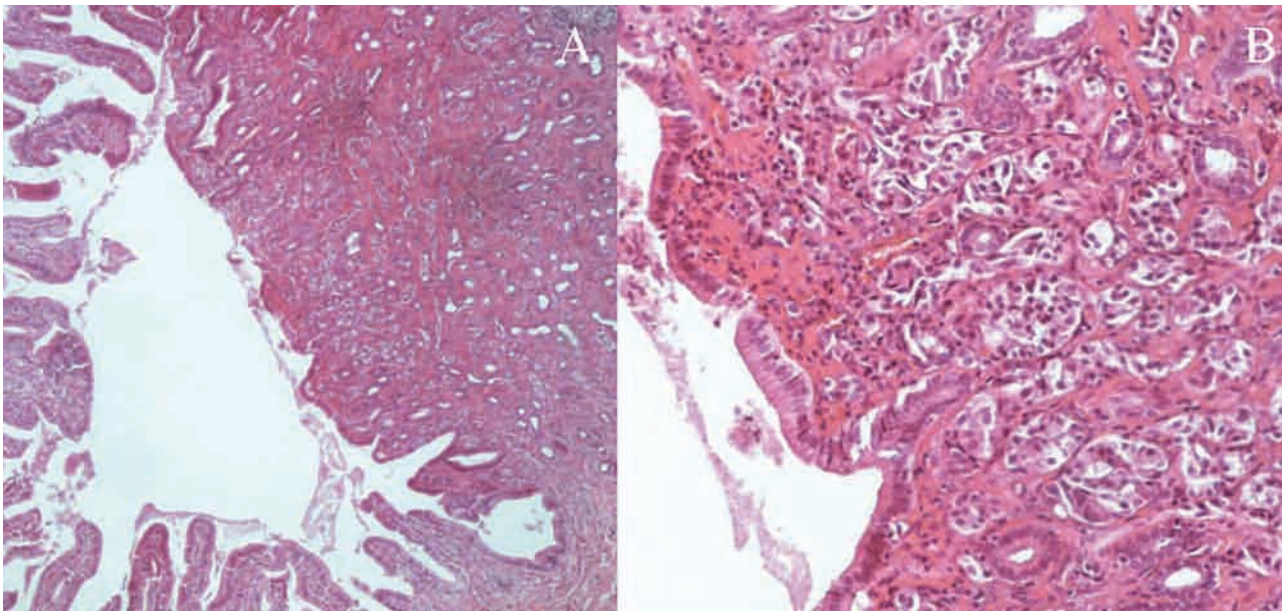

Fig. 1. — A. Carcinoid tumor of the cystic duct (H&E ×40). B. The neoplastic cells, usually small and rarely medium size with round relatively uniform nuclei and dense chromatin, were aligned in an organoid pattern.

biliary tree cancers (5,6). On the other hand NETs of the bile ducts are uncommon and their anatomic sites of presentation include the common bile duct (58%), the perihilar region (28%), the cystic duct (11%) and the common hepatic duct (3%) (3). The mean age of diagnosis is 47.5 years (range from 12 to 79 years) and there is a female predominance with the female to male ratio being from 1.05 to 2.2:1 (3,5,6). Clinically, NETs of the biliary tree usually present with painless jaundice (72.4%) followed by right upper quadrant pain (27.5%) and less commonly with pruritis (3,5,6). Manifestation with carcinoid syndrome is extremely rare (7), while a few patients had a slightly increased level of urinary 5-hydroxyindoleacetic acid (6). In rare cases they may be asymptomatic and discovered incidentally as in the present case. However the possibility that the biliary colic in our patient was not caused by the microlithiasis but by the NET cannot be ruled out.

Preoperative diagnosis is seldom made (4.8%) and NETs are usually incidentally found during abdominal surgical intervention for other indication (5,6). Endoscopic or percutaneous brush cytology has a high incidence of false negative results due to the submucosal location of the tumor (5,6). Differential diagnosis includes mainly the cholangiocarcinoma, and rarely other tumors of the biliary tree such as adenoma, leiomyoma, paraganglioma, lipoma and granular cell tumor (6).

Macroscopically, NETs are yellowish small, firm submucosal tumors (2). Gastrointestinal NETs originate from the foregut, midgut and hindgut (2,8). Histopathologically, NETs are divided in three grades based on mitotic count and Ki67 index : 1) NET G1 (or carcinoid) with mitotic count less than 2 per 10 high power fields (HPF) and/or Ki67 index less than 2% 2) NET G2 with mitotic count 2-20 per 10 HPF and/or Ki67 index 3-20% and 3) NET G3 (also called neuroendocrine carcinoma or NEC) with mitotic count more than 20 per 10 HPF and/or Ki67 index more than 20% (1). The preset case is a G1 NET. Immunohistochemical staining may be positive for chromogranin, somatostatin, serotonin and gastrin (5,9,10).

The treatment of choice is aggressive surgical resection aiming to complete resection (3,5,6,11). The majority of bile ducts NETs are confined within the biliary tree and less than one third of cases present with distant metastases, most frequently to the lymph nodes and liver and rarely to the pancreas and gallbladder (3,5,6). NETs that are less than 1 cm in diameter are associated with a 2% risk of metastasis. In cases, where the diagnosis was made postoperatevily, during histopathologic examination of the resected specimen, like the present one, there is no evidence to support "second-look" surgery, either laparoscopic or open laparatomy (5). In the present case, as the tumor was less than 1 cm and had been completely resected we didn't perform "second-look" surgery. The role of adjuvant chemotherapy and radiotherapy is still under research (5,6).

Following the diagnosis of extrahepatic bile duct NET, thorough radiologic staging should be performed in order to exclude residual disease of distant metastasis. This includes abdominal CT or MRI or both, that are useful in detecting hepatic and lymph node metastasis (2,4,12,13). Also 111In-DTPA octreotide scintigraphy, which takes advantage of the fact that 90% of these tumors and their metastases possess somatostatin receptors in high density, should be used in order to detect

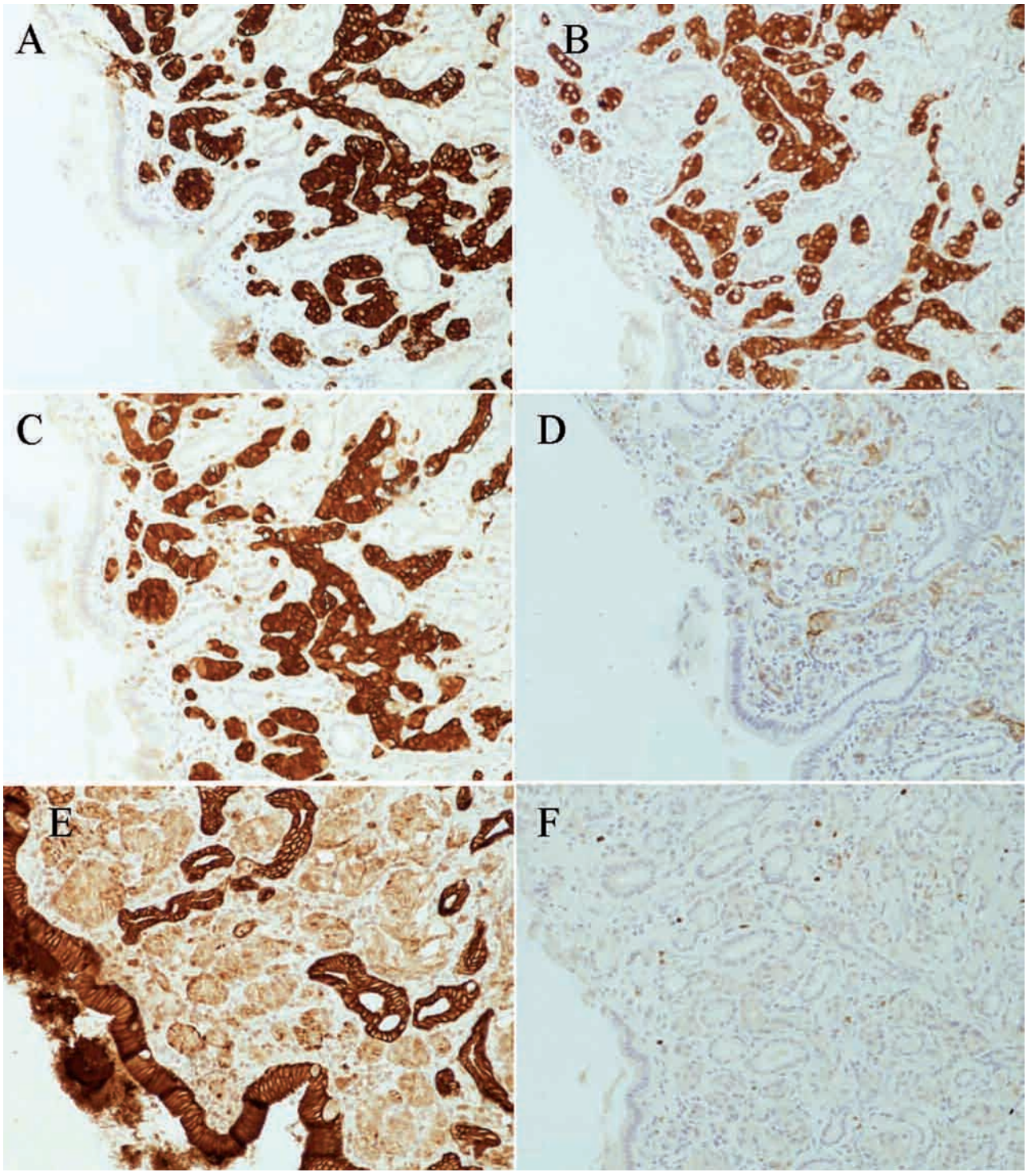

Fig. 2. — Neoplastic cells showed strong positivity for chromogranin (A ×200), synaptophysin (B ×200) and NSE (C ×200), mild positivity to CD 56 (D ×200) and CAM 5.2 (CK8/18) (E ×200, epithelial cells demonstrate strong positivity). The Ki-67 was very low, 1-2% (F ×200).

distance metastasis but not in all patients and especially in those cases where the risk of metastases in near zero (2,4).

Extrahepatic bile ducts NET are of low malignancy, exhibit limited propensity for local and metastatic spread, and present with favorable overall prognosis, with the 5-year survival rate being 60-100% in patients with localized tumors, while long term survival up to 20 years has been reported even in patients with distant metastases (3,5,6,14,15). Prognosis seems to be determined by tumor size, lymphovascular and perineural invasion, histological differentiation, quantitive assessment of Ki-67 reactive cells and invasion of adjacent tissues (3,6,16).

References

1. RINDI G., ARNOLD R., BOSMAN F.T., CAPELLA C., KLIMSTRA D.S., KLOPPEL G., KOMMINOTH P., SOLCIA E. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. *In :* BOSMAN F.T., CARNEIRO F., HRUBAN R.H., THEISE N.D. (ed). World Health Organization classification of tumours. 4th ed. WHO Classification of Tumours of the Digestive System. Lyon, IARC Press, 2010, pp. 13-14.
2. EVERS M.B. Small Intestine. *In :* TOWNSEND JR C.M., BEAUCHAMP R.D., EVERS B.M., MATTOX K.L. (ed). Sabiston Textbook of Surgery.17th ed. Philadelphia, Elsevier Saunders, 2004, pp. 1323-1400.
3. SETHI H., MADANUR M., SRINIVASAN P., PORTMANN B., HEATON N., RELA M. Nonfunctioning well-differentiated neuroendocrine tumor of the extrahepatic bile duct : an unusual suspect ? *Hepatobiliary Pancreat. Dis. Int*., 2007, **6** : 549-52.
4. YAO J.C., AJANI J.A. Management of neuroendocrine cancers of the gastrointestinal tract : carcinoid tumors. *In :* ABBRUZZESE J.L., EVANS D.B., WILLETT C.G., FENOGLIO-PREISER C. (ed). Gastrointestinal Oncology. New York, Oxford University Press, 2004, pp. 773-779.
5. STAVRIDI F., CHONG H., CHAN S., GOLDSMITH C., REDDY M., GLEES J. *et al*. Neuroendocrine tumour of the cystic duct : a case report and literature review. *J. Gastrointest. Cancer*, 2007, **38** : 32-3.
6. FELEKOURAS E., PETROU A., BRAMIS K., PRASSAS E., PAPACONSTANTINOU I., DIMITRIOU N. *et al*. Malignant carcinoid tumor of the cystic duct : a rare cause of bile duct obstruction. *Hepatobiliary Pancreat. Dis Int*., 2009, **8** : 640-6.
7. TODOROKI T., SANO T., YAMADA S., HIRAHARA N., TODA N., TSUKADA K. *et al*. Clear cell carcinoid tumor of the distal common bile duct. *World J. Surg. Oncol*., 2007, **5** : 6.
8. SCHRIEBER M.L., BASS B.L. Small intestinal neoplasms. *In :* GREENFIELD L.J., MULHOLLAND M.W., OLDHAM K.T., ZELENOCK G.B., LILLIMOE K.D. (ed). Essentials of Surgery : Scientific Principles and Practice. 2nd ed. Philadelphia, Lippincott Williams & Wilkins Publishers, 1997, pp 705-713.
9. CAGLIKULEKCI M., DIRLIK M., AYDIN O., OZER C., COLAK T., DAG A. *et al*. Carcinoid tmour of the common bile duct : report of a case and a review of the literature. *Acta Chir. Belg*., 2006, **106** : 112-5.
10. MAITRA A., KRUEGER J.E., TASCILAR M., OFFERHAUS G.J., ANGELES-ANGELES A., KLIMSTRA D.S. *et al*. Carcinoid tumors of the extrahepatic bile ducts : a study of seven cases. *Am. J. Surg. Pathol*., 2000, **24** : 1501-10.
11. CHAMBERLAIN R.S., BLUMGART L.H. Carcinoid tumors of the extrahepatic bile duct. A rare cause of malignant biliary obstruction. *Cancer*, 1999, **86** : 1959-65.
12. MENEZES AA., DIVER AJ., MC CANCE D., DIAMOND T. Carcinoid tumour of the extrahepatic bile duct – report of a case and literature review. *Ulster. Med. J*., 2004, **73** : 59-62.
13. JIMÉNEZ R., BEGUIRISTAIN A., RUIZ-MONTESINOS I., VILLAR F., MEDRANO M.A., GARNATEO F. *et al*. Intrahepatic biliary carcinoid. *Rev. Esp. Enferm. Dig*., 2007, **99** : 287-8.
14. SCHMITT T.M., BONATTI H., HAGSPIEL K.D., IEZZONI J., NORTHUP P., PRUETT T.L. Carcinoid of the bile duct bifurcation. *J. Am. Coll. Surg*., 2008, **206** : 399.
15. PITHAWALA M., MITTAL G., PRABHU RY., KANTHARIA C.V., JOSHI A., SUPE A. Carcinoid tumor of bile duct. *Indian J. Gastroenterol*., 2005, **24** : 262-3.
16. CHITTAL S.M., RA P.M. Carcinoid of the cystic duct. *Histopathology*, 1989, **15** : 643-6.