

CASE REPORT

Primary neuroendocrine tumors – an extremely rare cause of obstruction of extrahepatic bile ducts: a case report

ANDREI IONUȚ COSTIN¹⁾, ION PĂUN²⁾, MARIANA PĂUN³⁾, VLAD DENIS CONSTANTIN⁴⁾, FLORE VÂRCUȘ⁵⁾

¹⁾PhD Student, Department of Histology, University of Medicine and Pharmacy of Craiova, Romania

²⁾Department of Surgery, University of Medicine and Pharmacy of Craiova, Romania

³⁾Department of Gynecology, University of Medicine and Pharmacy of Craiova, Romania

⁴⁾Emergency Surgery Unit, "St. Pantelimon" Emergency Clinical Hospital, Bucharest, Romania

⁵⁾Surgical Clinic 2, "Victor Babeș" University of Medicine and Pharmacy, Timișoara, Romania

Abstract

Primary neuroendocrine tumors of the extrahepatic bile ducts are extremely rare – up to date, only 77 cases have been reported in the literature, which represents between 0.2–2% of all gastrointestinal carcinoid tumors. The paper focuses on the case of a woman patient, aged 37 years, admitted to the Clinic with the diagnosis of obstructive jaundice, unaccompanied by pain and where imaging indicates a tumor in the third average of the common bile duct (CBD). The surgery involved the excision of CBD, lymphadenectomy and restoring the biliodigestive continuity of Roux-en-Y hepaticojejunostomy. The histopathological and immunohistochemical examinations revealed the presence of a well-differentiated neuroendocrine tumor of CBD. Based on the case report and literature, we attempted to accurately identify and relate this type of tumor to other varieties encountered in the extrahepatic bile ducts, pointing out elements of a positive diagnosis, differential diagnosis, histopathology and immunohistochemistry, and referring to the therapeutic attitude, evolutionary methods and prognosis.

Keywords: neuroendocrine tumor, extrahepatic bile ducts, surgery, prognosis.

Introduction

Neuroendocrine tumors (NETs) originate in the embryonic neural crest cells called Kulchitsky cells, having the ability to secrete peptides and neuroamine and showing a changing clinical and biological behavior, depending on location, degree of differentiation and their secreting activity [1, 2].

Previously known in the literature as carcinoid tumors, the term was replaced by neuroendocrine tumors by the *World Health Organization* (WHO) in 2000 [1, 3].

According to the WHO classification, based on biological and histological criteria, these tumors fall into three grades [1, 3, 4]:

- well differentiated NETs (carcinomas) (low grade);
- moderately differentiated NETs (carcinomas) (intermediate grade);
- slightly differentiated NETs (carcinomas) (high grade), subdivided in their turn into two subgroups: (i) small cell neuroendocrine carcinomas; (ii) large cell neuroendocrine carcinomas.

Besides these pure neuroendocrine tumors, literature equally describes mixed exocrine–endocrine types, also called mixed adenoneuroendocrine carcinomas [4, 5].

They are most commonly located in the digestive tract, mainly in the ileum and vermiform appendix, however, neuroendocrine tumors can also be found in the bladder, prostate and ovary, kidney, bronchial tree, and even in soft tissues [2, 4, 5].

The paper is concerned with the interesting case of a young woman diagnosed and treated in our Clinic for a neuroendocrine tumor of the common bile duct.

Case presentation

Patient V.I., aged 37 years, from Ișalnița Village, Dolj County (Romania), with no significant history, was hospitalized in the IVth Surgery Unit, being transferred from the Infectious Diseases Unit with the diagnosis of obstructive jaundice.

Clinically, the patient showed jaundice accompanied by itching and vomiting, dark urine and pale stools.

On physical examination, mild right hypochondrium tenderness on deep palpation was revealed.

Laboratory results highlighted: total bilirubin (TB) 6.86 mg/dL, direct bilirubin (DB) 5.2 mg/dL, serum glutamic oxaloacetic transaminase (SGOT) 422 IU/L, alanine aminotransferase (ALT) 644 IU/L, gamma-glutamyl transferase (GGT) 1370 IU/L, cancer antigen (CA) 19-9 23 U/mL, normal carcinoembryonic antigen (CEA).

Abdominal ultrasonography indicated a normal dimension of the liver, of homogeneous structure, common bile duct (CBD) in the dilated hepatic hilum, having a diameter of 13 mm, showing a tissue-type formation in the third average, with low arterial vascular signal, natively sketched, with anteroposterior (AP) 15 mm, transversal diameter 20 mm and craniocaudal diameter 26 mm; dilated intrahepatic bile duct (IHBD); gallbladder without calculi, homogeneous pancreas, Wirsung and CBD to the head of the pancreas of normal caliber.

The cholangio-magnetic resonance imaging (MRI) confirmed the above data. The diagnosis of jaundice by CBD tumor led to surgery.

Intra-operatively, following the CBD dissection, an oval tumor of approximately 2.5 cm on the longitudinal

axis was identified as located at about 2 cm below the confluence of the two hepatic ducts and at about 1.5 cm from the ampulla of Vater.

CBD tumor resection was performed, with portal lymphadenectomy and Roux-en-Y hepaticojejunostomy reconstruction. The excision part is shown in Figure 1.

The initial pathology on frozen section was reported as cholangiocarcinoma of the CBD.

The postoperative evolution was favorable and the patient was discharged on the 9th day. Microscopically, the tumor was composed of sheets of uniform cells with granular cytoplasm, central, round nuclei and coarse claustrated chromatin. It was no evidence of necrosis, vascular or perineural invasion.

Histopathology showed the typical rosette appearance

of a neuroendocrine tumor (Figure 2). Lymph nodes were not involved.

The immunohistochemical analysis showed neoplastic cells diffusely positive for neuron specific enolase (NSE), chromogranin A, synaptophysin; the percentage of Ki-67-positive cells was assessed by scoring a minimum of 800 tumor cells in areas of highest immunostaining, giving a labeling index of 2% (Figures 3–6).

Serotonin plasma and 5-hydroxyindoleacetic acid (5-HIAA) in 24 hours urine were within the normal range.

The patient was referred to the Oncology Unit, with no recommendation of any complementary treatment.

The patient's evolution two years after surgery is favorable, with the absence of any recurrence and without secondary determinations.



Figure 1 – Resected specimen.

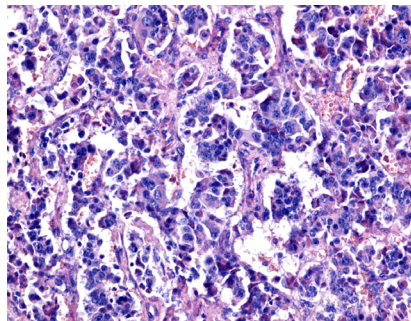


Figure 2 – Histopathology showed the typical rosette appearance of a neuroendocrine tumor. Hematoxylin–Eosin staining, ×200.

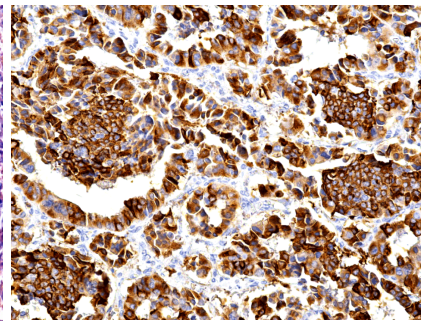


Figure 3 – Immunoreactivity for chromogranin in tumor cells. Immunohistochemical staining, ×200.

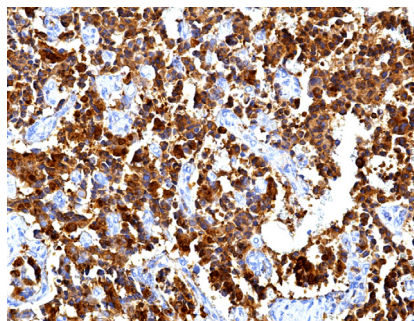


Figure 4 – Immunoreactivity for NSE in tumor cells. Immunohistochemical staining, ×200.

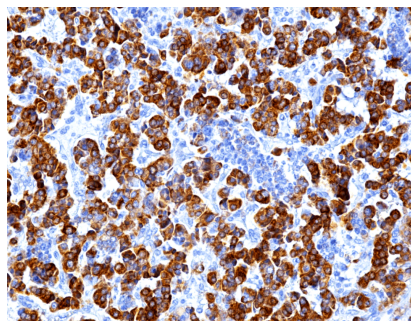


Figure 5 – Immunoreactivity for synaptophysin in tumor cells. Immunohistochemical staining, ×200.

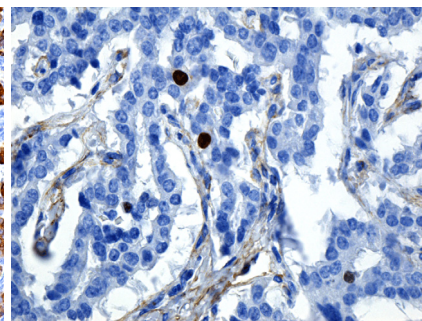


Figure 6 – Immunoreactivity for Ki-67 present in less than 2% from tumoral cells. Immunohistochemical staining, ×400.

Discussion

Neuroendocrine tumors of the bile duct are extremely rare and represent between 0.2% and 2% of all gastrointestinal neuroendocrine tumors [2, 3, 6, 7].

Until 2012, only 77 such cases had been described in the literature, which is explained by the paucity of enterochromaffin (EC) cells in the bile duct, at the origin of neuroendocrine tumors [2].

The chronic inflammation of the bile duct epithelium favors metaplasia of these EC cells and the subsequent occurrence of carcinoid tumors [2, 6].

In 1929, Joel *et al.* report the first case of a carcinoid tumor in the gallbladder [4, 6].

In 1959, Davies describes the existence of a carcinoid in the distal CBD and pancreatic duct, which is considered a periampullary carcinoid [4, 6].

In 1961, Pilz describes the first carcinoid tumor at the level of CBD [2, 3, 6].

The most common localization of NETs, except the gallbladder and ampullary region, is the CBD, representing 57.14% of cases, followed by the hilar confluence amounting to 27.28% of the cases, the cystic duct – 9.1%, common hepatic duct – 5.12% of the cases and the left hepatic duct – 1.23% of the cases [2, 3, 8, 9].

As the case reported confirms, NETs in the bile duct mainly occur in females aged between 6–79 years, the average age of occurrence being 47 years old [2, 3, 5, 7].

These tumors evolve asymptotically for a while, being diagnosed, sometimes, accidentally, during an abdominal imaging test [ultrasonography (US), computed tomography (CT), etc.] or by the occurrence of obstructive jaundice, as happened with our patient, occurring, more often than not, while in good health.

The jaundice is described in 63.4% of the patients, whereas other clinical symptoms such as abdominal pain or weight loss are reported rarely, often in connection with the tumor invasion of adjacent structures or metastases [2, 3, 10].

As with our patient, most neuroendocrine tumors of the bile duct were non-secreting, the carcinoid syndrome being recorded only in four cases, accompanied by high values of the 5-HIAA in the 24-hour urine [2].

Although in the majority of cases, patients received abdominal imaging such as abdominal ultrasound, CT scan, endoscopic retrograde cholangio-pancreatography (ERCP), echoendoscopy or percutaneous transhepatic cholangiography, the correct diagnosis was established, in most cases, in the postoperative stage, following the histological and immunohistochemical examinations of the excision parts [2, 11].

Provided that the incidence of extrahepatic bile colangiocarcinomas is very high, in most cases, with obstructive jaundice and CBD tumors identified during imaging, are suspected in the preoperative stage as showing such a tumor [6, 12].

In the most of cases, is nearly impossible to distinguish, preoperatively or even during surgery between biliary NETs and cholangiocarcinomas.

Unlike cholangiocarcinoma, biliary NETs occur more commonly in younger women patients, the aggressive local invasion is rare and the metastases occur in less one-third of cases.

A correct preoperative diagnosis of neuroendocrine tumors in the CBD could take place after the cytological examination of the product obtained by brush cytology, but in such cases, the incidence of false negative results is rather high due to the submucosal location of the tumors [3, 13].

However, such a diagnosis can be suspected in cases in which the dosage of 5-HIAA in the urine over 24 hours shows high values.

The treatment of the neuroendocrine tumors of the biliary ducts depends on the location of the tumor and the extent of the disease [10, 14].

The surgical resection is the primary treatment for biliary NETs and the only therapy that offers the chance of cure.

The proximal common bile duct, hepatic duct and cystic duct carcinoids may be treated by en bloc resection of the tumor and adjacent bile duct, regional lymphadenectomy and Roux-en-Y reconstruction hepatico-jejunostomy [3, 10, 11].

Taking into consideration that in our patient the tumor was localized in the third average CBD, we resorted to this type of intervention.

Partial hepatectomy may be required when the liver is involved.

Due to the difficulty in differentiating distal CBD tumors from periampullary or pancreatic head ones, in these cases, pancreatoduodenectomy is recommended.

Post-surgical histological exam and immunohistochemical stainings for neuroendocrine markers (chromogranin, synaptophysin, NSE and CD56) are useful in establishing the correct diagnosis [4, 15, 16].

In our reported case, considering that the tumor was localized without metastatic spread, it was not required to associate a complementary treatment.

Adjuvant chemotherapy is recommended especially for patients with poorly differentiated neuroendocrine tumors considered aggressive evolving forms in cases where the tumor has spread to nearby structures and/or is accompanied by lymph node or visceral metastases [6, 7].

In cases where the carcinoid syndrome is present, administration of somatostatin analogues (octreotide) enables a significant improvement of symptoms with improved quality of life [17–19].

In patients with carcinoid syndrome resistant to the octreotide therapy, its association with interferon may be beneficial in relieving symptoms as this combination may, in some cases, stabilize the tumor or even cause tumor regression [1, 2, 17, 19].

The limited statistical data in the literature indicate that the neuroendocrine tumors of the biliary ducts, in most cases, seem to be slow growing and have a limited propensity for local and metastatic spread.

The prognosis of these tumors is generally favorable with a high rate of long-term survival, more particularly, in cases in which curative surgical resection was possible [2, 3, 6, 7].

In some cases in advanced stages, even if inoperable, the correct administration of adjuvant therapy (chemotherapy, somatostatin analogues, interferon) may improve prognosis with increasing survival time [1, 2, 17–19].

Up to date, it can be said that there is no absolute histological criterion to assess the potential for malignancy of the neuroendocrine tumors of the bile ducts.

Nevertheless, the tumor size seems to correlate best with the probability of metastasis [3, 16].

On the other hand, lymphovascular invasion is a common finding in these tumors, and the quantitative assessment of the Ki-67 reactive cells may allow an assessment of prognosis and survival time [1, 3].

However, in general, most authors agree that the curative surgical resection represents the decisive factor of prognosis in patients with neuroendocrine tumors of the extrahepatic bile ducts [3, 14, 15].

✎ Conclusions

Carcinoid tumors of the extrahepatic bile ducts are extremely rare and, usually are non-secreting tumors. The preoperative diagnosis seems to be difficult, symptoms and imaging often raising suspicion of cholangiocarcinoma. The correct diagnosis, usually in the postoperative stage, presupposes histopathological and immunohistochemical studies. The curative surgical resection secures a favorable prognosis and long-term survival. Even in advanced stage or inoperable cases, chemotherapy and possibly octreotide associated with interferon may improve prognosis.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Corresponding author

Ion Păun, Associate Professor, MD, PhD, Department of Surgery, University of Medicine and Pharmacy of Craiova, 2 Petru Rareș Street, 200349 Craiova; Surgery Unit, Railway Clinical Hospital, 6 Știrbei Vodă Street, 200374 Craiova, Romania; Phone +040723–347 572, e-mail: dripaun@gmail.com

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