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Case Report

Neuroendocrine Tumor of the Common Bile Duct: Case Report

Ricardo Fernández-Ferreira[a] Emilio Medina-Ceballos[b]
Pamela Denisse Soberanis-piña[a] Emilio Conde-Flores[a]
Andrés Mauricio Arroyave-Ramírez[a]
Carlos Daniel Izquierdo-Tolosa[a] Daniel Motola-Kuba[a]
Jose Manuel Ruiz-Morales[a] Rita Dorantes-Heredia[b]

[a]Oncology Medicine Department, Comprehensive Oncology Center "Diana Laura Riojas de Colosio", Medica Sur Clinic & Foundation, México City, Mexico; [b]Service of Anatomical Pathology, Medica Sur Clinic & Foundation, México City, Mexico

Keywords
Neuroendocrine tumors · Kulchitsky cells · Extrahepatic bile duct · Surgical resection · Immunohistochemical analysis

Abstract
Carcinoma of the extrahepatic biliary tract accounts for <2% of all cancers. Neuroendocrine tumor of the extrahepatic bile duct is very rare, and there are <200 cases reported since 1959. The preoperative diagnosis is infrequent (5.12%). The definite diagnosis relies on postoperative pathology which utilized immunohistochemistry study on many biomarkers to diagnose the histological subtypes of neuroendocrine neoplasms, such as chromogranin A, synaptophysin, and neuron-specific enolase. When the primary tumor has no metastases, radical removal of the lesion appears as curative treatment. The treatment of the carcinoid syndrome or other functioning syndrome is the first priority. We report a case of a 12-year-old Mexican woman with neuroendocrine tumor of the extrahepatic bile duct (common bile duct neuroendocrine tumor) seen in our hospital. Resection of the common bile duct, cholecystectomy, end to side Roux-en-y hepaticojejunostomy, and portal lymphadenectomy was performed. A review of the pertinent literature was performed. Given the rarity of the disease, treatment principles are based mainly on retrospective series and case reports. We present the eighth case in adolescence in the literature.

Correspondence to:
Ricardo Fernández-Ferreira, ricardo.fdez.ferreira@comunidad.unam.mx

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Introduction

Carcinoma of the extrahepatic biliary tract accounts for <2% of all cancers. According to the analysis of 13,715 neuroendocrine tumor (NET) cases of all organs of the digestive system by Modlin et al. [1], the incidence of neuroendocrine tumors of the extrahepatic bile ducts (EBNETs) was 0.32%.

A multitude of terms have been used to describe EBNETs including "malignant carcinoid," "apudoma," "carcinoid," "argentaffin tumor," "adenoendocrine carcinoma," "atypical carcinoid," and "endocrine cell carcinoma." Carcinoid is the most common term used to describe these tumors before 1996, when the WHO initially by Kloppel et al. [2] and subsequently by Capella et al. [3] had agreed to replace it with the broader term "NET."

The "carcinoid tumors" have been renamed by the WHO into "NETs," in order to designate all gastrointestinal lesions with evidence of endocrine differentiation. Three NET categories are defined regarding the grade (G): G1, mitotic index count <2 mitoses per high-power field (HPF) and/or Ki-67 index <2%; G2, mitotic index count 2–20 mitoses per HPF and/or Ki-67 index 3–20%; G3, mitotic index count >20 mitoses per HPF and/or Ki-67 index >20% [4].

In 1959, the first EBNET was reported by Davies [5]. From 1959 up to 2021, articles describing <200 cases were published.

Here, we report a case of EBNET (common bile duct NET) seen in our hospital. To date, the final diagnosis is made after surgery by pathology and immunohistochemistry findings. The present analysis of the existing published cases elucidates many aspects of these tumors.

Case Report

A 12-year-old Mexican woman presented to our hospital with jaundice, pruritus, acholia, and coluria, with laboratory studies that reported elevation of direct bilirubin, alkaline phosphatase, and gamma glutamyltransferase. A bile duct ultrasound was performed where dilation was observed in the bile duct, for which an endoscopic retrograde cholangiopancreatography was indicated, where a polyp was reported that conditioned an increase in the volume of 50% of the intra- and extrahepatic bile duct, for which a prosthesis was placed (Fig. 1A, B, C). In this intervention, biopsies of the bile duct were taken in which the tissue was very scarce, so a diagnosis could not be established. The patient was discharged with outpatient management with ursodeoxycholic acid presenting clinical improvement for 1 year. The patient attended again this time due to the reappearance of obstructive liver symptoms. Magnetic cholangioresonance was performed, in which dilation of the bile duct was reported (Fig. 1D). Therefore, it was decided to perform an exploratory laparotomy where a resection of the common bile duct, cholecystectomy, end to side Roux-en-y hepaticojejunostomy, and portal lymphadenectomy was carried out.

On gross examination by the pathology laboratory, a lesion was identified within the common bile duct, which obstructed the lumen and caused a dilation of the pathway to the proximal edge of the liver. The lesion corresponds to a polyp with a broad base measuring 1.9 × 1.8 × 1.6 cm, which was exophytic and was still firmly attached to the wall, and the cut was solid (Fig. 2A). The microscopic study showed that the tumor had multiple growth patterns. It had areas made up of solid sheets of cells, areas with growth of papillary architecture, and areas with trabecular growth (Fig. 2B). The cells were medium in size with round nuclei with an eosinophilic cytoplasm, and the chromatin was distinguished by a granular appearance (Fig. 2C). The tumor showed intravascular, lymphatic, and perineural invasion. In addition, it invaded 6 mm of the bile duct wall. Immunohistochemical stains were performed in which

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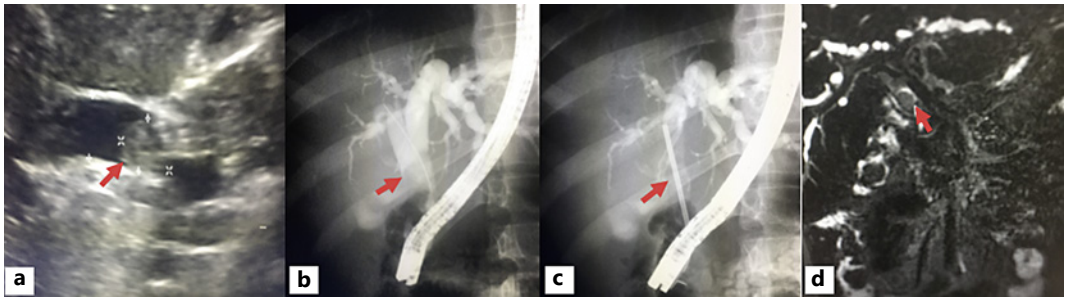

Fig. 1. The bile duct ultrasound shows dilation in the common bile duct (**a**), endoscopic retrograde cholangiopancreatography reported a polyp that conditioned an increase in the volume of 50% of the intra- and extrahepatic bile duct (**b**), prosthesis was placed (**c**), and magnetic cholangioresonance was performed, in which dilation of the bile duct was reported (**d**).

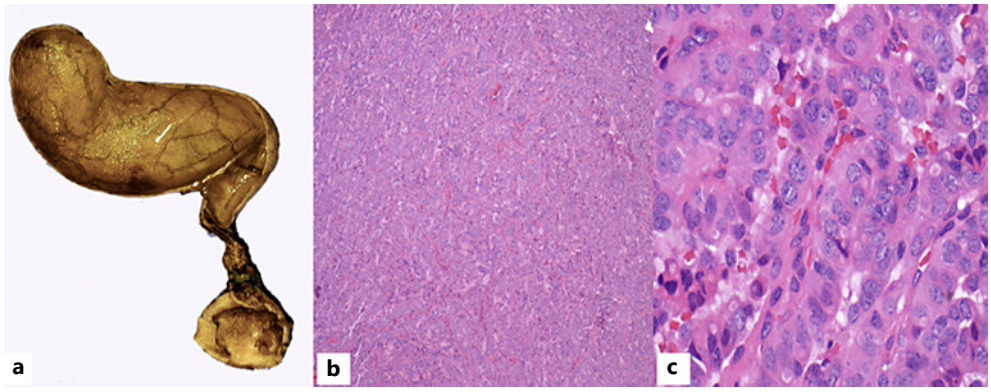

Fig. 2. The lesion corresponds to a polyp with a broad base measuring 1.9 × 1.8 × 1.6 cm, which was exophytic and was still firmly attached to the wall, and the cut was solid (**a**). The microscopic study showed that the tumor had multiple growth patterns. It had areas made up of solid sheets of cells, areas with growth of papillary architecture, and areas with trabecular growth (**b**). The cells were medium in size with round nuclei with an eosinophilic cytoplasm, and the chromatin was distinguished by a granular appearance (**c**).

the neuroendocrine markers were intensely positive (chromogranin, synaptophysin, and CD56) (Fig. 3). Likewise, MyoD1, CD45, CK7, and CK20 were performed to rule out differential diagnoses of rhabdomyosarcoma, neoplasia of lymphoid origin, and adenocarcinoma. The diagnosis of NET was concluded. Ki-67 was positive in 15% of neoplastic cells, which qualifies it as grade 2.

Discussion

NETs are distinct neoplasms with characteristic histological, clinical, and biological properties. Recent years have witnessed an increase in the incidence of NETs (3.65/100.000/year) which may be due to either actual increase in incidence or improved diagnostic tools [6, 7].

NETs may arise from argentaffin or Kulchitsky cells, which are now believed to be endoderm in origin. Kulchitsky cells, which are present throughout the gastrointestinal tract, are extremely scarce in the bile duct mucosa, possibly explaining the rarity of EBNETs. Chronic inflammatory changes within the bile duct may result in metaplasia of the scattered endo-

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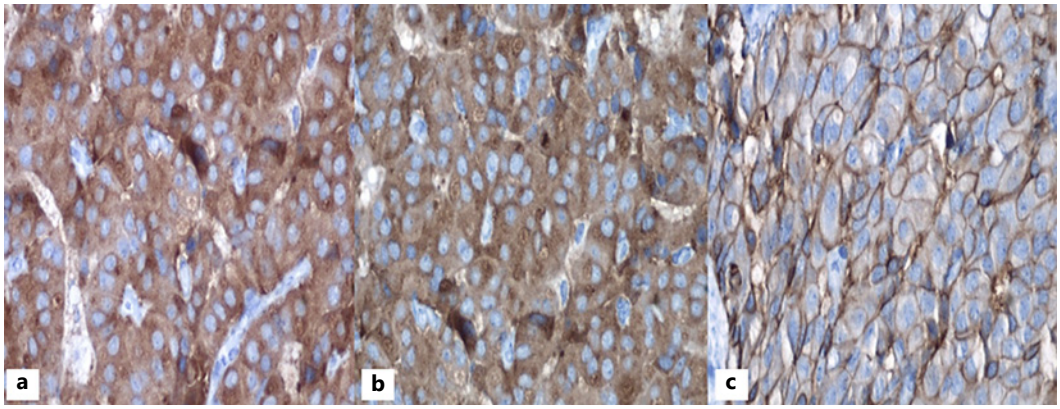

Fig. 3. Immunohistochemical stains were performed in which the neuroendocrine markers were intensely positive for chromogranin (**a**), synaptophysin (**b**), and CD56 (**c**).

crine cells in the biliary epithelium, which are precursors to EBNETs [8–11]. They can be associated with hereditary endocrine syndromes (MEN and Von Hippel Lindau); they can occur at any age, and the incidence is slightly higher in men than women [12, 13].

In a literature review regarding EBNET, Michalopoulos et al. [14] reported approximately 38 cases of NET from 1961 to 2013, and the median age was 47 years (range, 6–79 years), with a female (61.5%) predominance. Only 7 cases have been reported in adolescents to date. The tumors were symptomatic in 88.5% of patients. The symptoms were mostly related to tumor mass growth, invasion of adjacent structures, or metastases rather than hormone and vasoactive peptide secretion. The most common symptoms were jaundice (60.3%) and pruritus (19.2%), with 9% hormone- and vasoactive peptide-related symptoms. The most common sites for primary NETs are the gastrointestinal tract (73.7%) and bronchopulmonary system (25.1%) with only 0.1%–0.4% occurring in the extrahepatic bile ducts [1].

The most frequent sites of EBNET are the common hepatic duct and distal common bile duct (19.2%), followed by the middle of the common bile duct (17.9%), cystic duct (16.7%), and proximal common bile duct (11.5%) [14]. Also, Liu et al. [15] found other 10 including their case and reported 48 cases of NET in 2018.

The preoperative diagnosis was reported to be feasible in only 4 of 78 cases (5.12%) [14]. Preoperative decompression of the biliary tree with stent placement still is controversial [15].

The definite diagnosis relies on postoperative pathology which utilized immunohistochemistry study on many biomarkers to diagnose the histological subtypes of neuroendocrine neoplasms, such as chromogranin A, synaptophysin, and neuron-specific enolase [15–17].

The NET, as it is named, has the potential to secrete numerous hormonal substances such as serotonin, gastrin, somatostatin, vasoactive intestinal peptide, glucagon, and insulin, but usually these substances are not measured through preoperative diagnosis course because of the absence of detectable serum markers and the usual lack of hormonal symptoms [6–14]. In Little et al. [18] case, urinary 5-hydroxyindoleacetic acid was measured preoperatively and led to diagnosis. Also, gastrin serum level was found to be increased in Martignoni et al. [19] study.

Unlike carcinoma of the extrahepatic bile duct wherein two-thirds of patients present with metastatic disease, one-third of patients with EBNET present with metastases either to the local lymph nodes (19.23%) or to the liver (16.7%) [14, 20]. Finally, total surgical resection is feasible in the vast majority of NETs, while curative resection of cholangiocarcinoma is

feasible in only one-third of all cases. The optimal treatment for patients with NET or NEC is controversial as most of the current literature available comes from case reports and small case series, without comparable control groups [1–20].

When the primary tumor has no metastases, radical removal of the lesion appears as curative treatment. Surgical resection of the primary and the metastases, when possible, remains the only curative treatment in patients with GEP-NETs. However, many patients are diagnosed once unresectable metastases have occurred, and the treatment is then more challenging [21, 22].

The treatment of the carcinoid syndrome or other functioning syndrome is the first priority. Following this, different options are available in this situation ranging from close surveillance for indolent tumors, through liver-directed treatment (radiofrequency or transarterial embolization) to systemic therapy (somatostatin analogs or interferon, cytotoxic and molecular targeted therapies, and radionuclide treatment); however, no direct comparison between these strategies exists [20–23].

EBNETs have great variety in their aggressiveness. It is difficult to assess the prognosis of these tumors since the cases are rare, and long-term follow-up is often unavailable. In view of available data, these tumors seem to have better prognosis than bile duct carcinomas after radical surgical treatment [24].

Those with typical neuroendocrine differentiation and minimal atypia (previously known as carcinoids) tend to be indolent in their behavior, whereas atypical NETs may have more poorly differentiated or aggressive characteristics and worse prognosis [25]. Although malignant EBNETs are of an aggressive nature, they also tend to be less aggressive than cholangiocarcinoma [26]. There are no absolute criteria for judging the malignant potential of EBNETs [27]; however, the size of the tumor, the presence of lympovascular invasion, and the quantitative assessment of Ki-67-reactive cells help to determine prognosis.

Conclusion

EBNET (common bile duct) is very rare. We present the eighth case in adolescence in the literature. Surgical resection of the primary tumor was performed, and the definitive diagnosis by pathology was reported.

Acknowledgment

Thanks are due to the Southern Medical Hospital for their support in data collection.

Statement of Ethics

The patient was a minor and died, so her mother signed the written informed consent to publish her daughter's case (including the publication of images). The study is exempt from ethics committee approval because only a review of the clinical record was carried out, and it was not an experimental study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Ricardo Fernández-Ferreira contributed to the conception of the case, analysis and critical revision of the content, and the final approval of the version to be published. Emilio Conde-Flores, Daniel Motola-Kuba, Pamela Denisse Soberanis-piña, Andrés Mauricio Arroyave-Ramírez, Carlos Daniel Izquierdo-Tolosa, and Jose Manuel Ruiz-Morales contributed to the critical revision of the content and the final approval of the version to be published. Rita Dorantes-Heredia and Emilio Medina-Ceballos carried out an exhaustive review of the histopathological characteristics of cancer and analysis of the article. All authors agree to be responsible for all aspects of the job and ensure that questions related to the accuracy or completeness of any part of the job are properly investigated and resolved.

Data Availability Statement

Data supporting the findings of this study are openly available in the clinical file of the southern Medical Hospital, with Registration No. 851862. Additional inquiries can be directed to the corresponding author.

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