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Management of neuroendocrine tumors of the extrahepatic bile duct: Case report and review of the literature

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Abstract

Neuroendocrine tumors of the extrahepatic bile duct (EBNETs) are exceedingly rare neoplasms, whose diagnostic and therapeutic process can be challenging. We present the case of a 58-year-old EBNET patient successfully treated at our Institution, followed by a systematic review of the literature on the surgical management of these rare tumors.

Keywords: neuroendocrine tumor; biliary neoplasm; carcinoid; biliary tract obstruction.

Case presentation

Neuroendocrine tumors (NETs) represent a rare, heterogeneous group of neoplasms with a distinct functional and biological behavior depending on their anatomic location, tumor size and clinical symptoms [1]. More than 50% of NETs arises in the gastrointestinal tract, being the appendix, the small bowel and the rectum the most common locations [2]. NETs located within the extrahepatic bile duct (EBNETs) are amongst the rarest primary sites, accounting for 0.2%-2% of all such malignancies [3,4] .

Obtaining a preoperative diagnosis of these tumors is difficult. Indeed, the majority of cases reported in the literature are diagnosed only after surgery, on the final pathological examination of the surgical specimen. Plasmatic Chromogranin A (CgA) and urinary 5-hidroxyindole acetic acid (5-HIAA) are slightly specific markers that can be used in combination to hypothesize the presence of NETs. Nevertheless, since, the majority of EB-NETs are non-functioning neoplasms, these markers may not be produced, secreted and therefore detected. Computed Tomography (CT) scan and Magnetic Resonance Cholangiopancreatography (MRCP) are the recommended imaging exams to stage EB-NETs and to plan the operative strategy. However, no specific CT or MRCP findings allowing distinguishing between EBNETs and other biliary neoplasms have been described so far. More sensitive and specific radiological techniques are available. Above all, positron emission tomography (PET) with radioactively labeled somatostatin analogues (like Ga68 DOTA-TATE, DOTATOC and DOTANOC) can be useful in case of clinical suspicion of EB-NETs, in both localized and metastatic settings, with a reported sensitivity and specificity of 81% and 90%, respectively [5]. The accuracy of endobiliary brush cytology for the preoperative diagnosis of biliary disease has been widely discussed [6], but its sensitivity for biliary tree tumors is limited. This particularly applies to EBNETs, considering the submucosal localization of the lesion [7,8]. Finally, fine needle aspiration cytology (FNAC)

and biopsy (FNAB) could be an helpful diagnostic tools [8], however in most cases a surgical exploration is still mandatory, in the suspicion of cholangiocarcinoma.

From a surgical standpoint, the resection of the extrahepatic bile ducts with portal lymphadenectomy and Roux-en-Y hepaticojejunostomy provides radical tumor clearance in most cases. In very selected patients a more extensive resection may be required, with various degrees of hepatic or pancreatic resection according to the tumor site.

In this paper, we present the case of a 58-year-old patient with an EBNET treated at our Institution. Moreover, we performed a systematic review of the literature on the surgical management of these rare neoplasms.

Case report

A 58-year-old man with history of type 2 diabetes and polycythaemia vera presented to our Hospital complaining of epigastric pain. Symptoms had started one month earlier. An Esophago-Gastro-Duodenoscopy (EGDS) showed mild gastritis (negative for *Helicobacter pylori*). Abdominal US demonstrated the presence of a mass (28 x 28 mm) located within the extrahepatic bile duct, causing diffuse dilatation of the intrahepatic biliary system. Despite the degree of ductal dilation, liver function tests and serum markers of cholestasis were within the normal ranges. The levels of alpha-fetoprotein, CA 19-9 and CEA were unremarkable. Endoscopic Ultrasound (EUS) showed a 28 mm hyperechoic lesion, with arterial and venous contrast enhancement after injection of SonoVue® contrast-agent; EUS confirmed the dilation of both right and left hepatic ducts, encompassing the cystic and the common bile duct, and also detected the presence of two reactive nodes within the hepatoduodenal ligament. A Fine Needle Biopsy (FNB) was performed and pathological analysis reported signet-ring cells adenocarcinoma. Since the patient did not present with jaundice, Endoscopic Retrograde Cholangiopancreatography (ERCP) was not performed. Abdominal CT-scan and MRCP revealed a mass of 28 x 24 mm in the common bile duct, without any suspicious nodes nor distant metastases.

The case was submitted to our Institutional Board and the patient was considerate candidate for exploratory surgery, followed by a bile duct resection, eventually associated with extended pancreatic or liver resection (established through intraoperative frozen section assessment of surgical margins).

At the laparotomic abdominal exploration, there was no evidence of carcinomatosis or distant metastases. The extrahepatic bile duct and the gallbladder were resected, and a radical lymphadenectomy of the liver pedicle was performed. The proximal and distal common bile duct margins were negative for malignancy on frozen section analysis, so a Roux-en-Y hepaticojejunostomy was finally performed. The postoperative course was unremarkable, and the patient was discharged on the post-operative day 6.

The final pathological analysis (Figure 1) demonstrated a G2 EBNET of 35 x 30 x 25 mm, Synaptophysin++, CgA+, infiltrating both the hepatic and the cystic duct, with ulceration of the mucosal layer. The lesion had solid-trabecular and pseudo-glandular growth pattern. The mitotic index was 2 for 10 high power fields, and Ki-67 labeling index was 5%. A neural invasion, but no vascular invasion, was detected. Lymph nodes examination did not detect any metastases.

Thus no adjuvant therapy was proposed by our Board. 6- and 12-month CT scans showed no evidence of local recurrence or distant metastases. At the 16-month follow-up, the patient is in good health, completely asymptomatic and with normal blood chemistry tests.

Review of the literature

We aimed at conducting a comprehensive systematic review and collecting data of all ENNETs cases which have been reported in the literature.

Materials and methods

The review of the literature was conducted through a systematic approach, following the PRISMA statements checklist (Figure 2). The following online databases were consulted: MEDLINE (through PubMed), EMBASE, Google Scholar, Cochrane and ProQuest Dissertations, and Thesis Database.

In order to increase the accuracy in identifying relevant articles, a research equation was formulated for each database, using specific keywords and/or MeSH terms (i.e., "neuroendocrine tumor", "Carcinoid", "Bile Duct"). In addition, bibliography from both eligible studies and relevant review articles (not included in the systematic review) was crosschecked in order to identify additional reports. A grey literature search was also performed using the OpenGrey database.

No time restrictions were applied. Relevant articles were defined as those written in English and reporting at least the following clinical, radiological and pathological patients' characteristics: age, gender, tumor location and size, symptoms, presence of metastases, time of diagnosis, treatment, immunohistochemistry, pathology, and follow-up data.

The studies eligible for inclusion, e.g., case report, case series have been all those answering to specific research question "How to manage successfully EBNETs patients?"

Reports of tumors involving intra-hepatic biliary ducts, liver parenchyma, gallbladder, and Vater region were excluded. Reports of Neuroendocrine Carcinomas (NEC) and mixed tumors, including both NET and adenocarcinoma features, were also excluded. Two reviewers (LP and FM) independently retrieved, screened and analyzed the selected studies. Conflicts between the two independent reviewers were solved with discussion with a third one (RR). A quality assessment and risk of bias of every study selected has been performed using tool described by Murad et al.

Results

Studied population

After removal of duplicates, the literature search identified a total of 763 articles. Of these, 619 were excluded upon title and abstract evaluation because they were not pertinent to topic. Out of the remaining 143 articles that underwent full-text evaluation, 49 were ruled out because they did not meet the inclusion criteria. Therefore, 94 articles, ranging from 1959 to

2020, were finally included in our systematic review (Table 1). Overall, 95 patients diagnosed with EBNETs were considered, 37 men (38.95%) and 58 women (61.05%). The mean age at the diagnosis was 47.48 ± 17.3 years. The main characteristics of the pooled population are summarized in Table 2.

Symptoms

Most patients were symptomatic, (n= 89, 92.7%), being jaundice the most frequent symptom (n=61, 65.6%). Other aspecific symptoms reported were abdominal pain or discomfort, nausea, vomiting, and pruritus; they were related to the compression of the bile duct or to the presence of a growing mass in the right hypochondrium.

The great majority of the neoplasms were non-functioning NET. Only 5 cases (5,4%) were associated with hormone hypersecretion [9-14] and the serum levels of 5-hydroxyindoleacetic acid (5-HIAA) were slightly elevated in two cases [13,15]; however, a true carcinoid syndrome has never been reported in patients with EBNETs.

Tumor location

The most frequent location was the common hepatic duct in 37,9% of cases (n=36), followed by the middle portion of common bile duct (34,8 %) while the distal part of CBD was involved in 15 cases (15,7%). Cystic duct was involved in 14 cases (14,7%) and proximal common bile duct (11,6 %). The tumor size has been reported 87 cases (91.5%), and its mean diameter was 2.2 cm (range, 0.2 – 6.2cm).

Type of intervention and outcomes

Several surgical options have been reported for patients with EBNETs, according to the location and extension of the neoplasm. The most frequently performed procedure was Biliary Duct Resection (BDR) and Roux-en-Y hepaticojejunostomy (RYHJ) (59.1%). Pancreatic and liver resections were performed in 27 patients (28.4%). Neoplasms were located within the cystic duct in 5 patients (5.3%), and cholecystectomy was considered an adequate treatment in all these cases. Finally, in 4 cases (4.2%) a radical resection was not possible and thus only biopsies were taken. The disease was metastatic at time of diagnosis in 26 cases (27.4%), with nodal involvement in 17 (17.7%) and liver metastases in 9 cases (9.4%). Immunohistochemistry staining was performed in all cases; the different markers expressed by the neoplasms are reported in Table 1.

The mortality rate in the postoperative period was low (n=1, 1.05%). Follow-up surveillance data were available for 71 patients (74.7%) and ranged from 1 to 240 months.

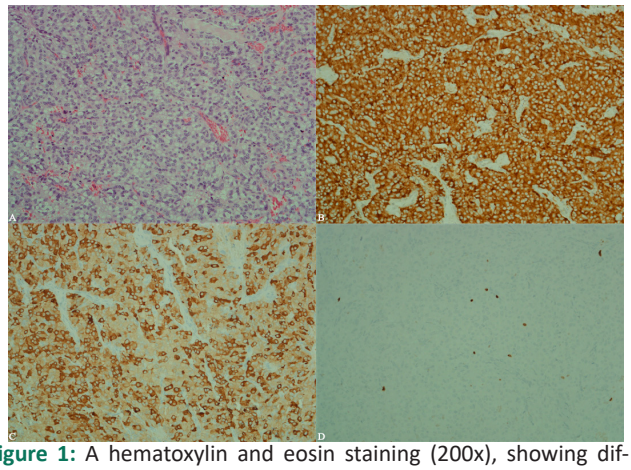

Figure 1: A hematoxylin and eosin staining (200x), showing diffuse and intense synaptophysin immunohistochemical staining (B, 200x), dyshomogeneous chromogranin A immunohistochemical staining (C, 200x) and 5% proliferative index (D, Ki67 immunohistochemical staining, 200x).

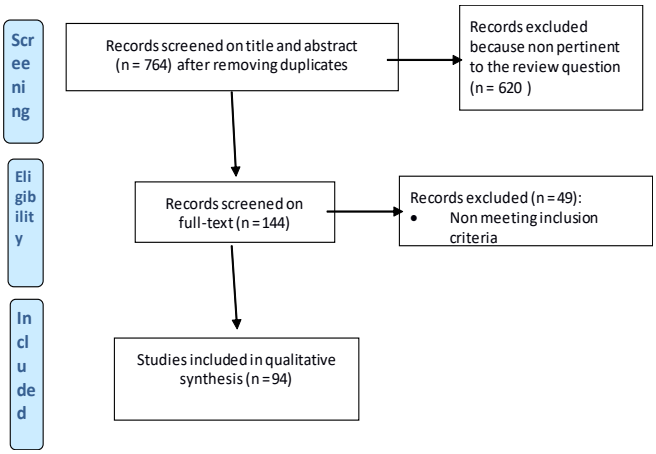

Figure 2: Flow chart of study search, selection and inclusion.

Tasble 1

1st Author	Year	Sex	Age	Location	Max size	Time of diagnosis	Final diagnosis	Treatment	Metastasis	F/up
Pilz (35)	1961	F	55	CBD		histology		Lap-B	0	
Little (16)	1968	F	41	PCBD		Preoperative (elevate urine 5-HIAA level)		Lap-B	1	3 weeks
Schwesinger (36)	1978	F	72	DCBD	2	histology			0	
Gerlock (37)	1979	M	32	PCBD	4	histology		BDR	0	
Vitaux (38)	1981	M	30	DCBD	1,5	histology		PD	0	48 months
Goodman (10)	1984	F	28	CD		histology		CH-C	0	9 m
Jutte (39)	1986	M	62	CHD	5,5	histology		BDR + right/left HJ	0	24.5 m
Gastinger (40)	1987	F	65	PCBD	1	histology		TR	1	5 m

Reinhardt (41)	1988	F	71	CBD	2,5	histology		PPPD	0	12 m
Fujita (42)	1989	F	55	CHD	2	histology		choledothomy, TR, T-tube	0	6 m
Chittal (43)	1989	F	46	CD	0,8	histology		Ch-C, partial BDR	0	36 m
Van der Wal (44)	1989	M	55	CHD-CD	4	histology		RYEJ	0	12 m
Bumin (45)	1990	F	38	CBD	2	histology		Ch-C, choledothomy, TR, T-tube	0	
Fellows (46)	1990	M	30	PCBD	1,5	histology		RYEJ	0	
Brown (47)	1990	F	35	CHD-B	2	histology		RYEJ	0	
Angeles-Angeles (48)	1991	F	39	CBD	1,5	histology		BDR + hepatico-duodenal anastomosis	0	42 m
Newman (49)	1992	F	15	DCBD		histology		PPPD	0	48 m
Rugge (50)	1992	F	64	CBD-CD	2,5	histology		RYEJ	0	12 m
Ueyama (51)	1992	F	60	CBD	1,5	histology		TR + segmentectomy	0	
Gembala (52)	1993	M	28	RHD-CHD	3	histology		Trisegmentectomy + HJ	0	
Sankary (53)	1995	F	47	PCBD	2	histology		Trisegmentectomy + HJ	0	48 m
Mandujano (11)	1995	F	53	DCBD	2,2	gastrinoma		CH-C + TR	0	8 m
Belli (54)	1996	M	78	PCBD	1,5	histology		RYEJ	0	15 m
Kopelman (33)	1996	F	44	CBD	0,5	histology		PPPD+ resection of left metastasis	1	18 m
Hao (12)	1996	M	42	CBD	1,3	histology		OLT	0	5 m
Meyer (55)	1997	F	56	CD		histology		CH-C, CDR	0	96 m
Shah (56)	1998	F	52	CD	0,5	histology		CH-C	0	
Oikawa (57)	1998	M	70	CBD-CD	2,5	histology		RYEJ+ liver resection	1	6 m
Bembenek (58)	1998	F	12	CHD	1,5	histology		RYEJ	0	9 m
Ross (59)	1999	F	65	DCBD	2,5	histology		PD	0	17 m
Perakath (60)	1999	F	36	CHD		histology		RYEJ	0	6 m
Hermina (61)	1999	M	69	CD	0,5	histology		RYEJ+Ch-C	0	14 m
Chamberlain (4)	1999	F	37	CHD-B	2,7	histology		RYEJ	0	96 m
Martignoni (62)	1999	M	60	CHD	1,3	gastrinoma		TR+T tube	0	36 m
Aronsky (63)	1999	F	64	CD	0,4	histology		RYEJ+Ch-C	0	47 m
Aronsky (63)	1999	F	51	CD		histology		RYEJ+Ch-C+ liver resection	0	49 m
Chan (64)	2000	M	14	CHD-B	2,8	histology		RYEJ+PTBD	0	36 m
Juturi (65)	2000	M	43	DCBD	4	histology		PD	0	42 m
Maitra (66)	2000	F	42	CBD	1,1	histology		RYEJ	0	132 m
Maitra (66)	2000	F	61	CHD-B	2	histology		RYEJ+Ch-C	0	48 m
Maitra (66)	2000	F		CBD	1,4	histology		RYEJ	0	120 m
Maitra (66)	2000	F	37	CHD	2,7	histology		RYEJ+Ch-C	0	24 m
Maitra (66)	2000	F	67	CHD	2,5	histology		RYEJ+Ch-C	0	24 m
Turrion (67)	2002	F	51	CHD-B	2,7	histology		OLT	0	18 m
Pawlik (68)	2003	M	59	PCBD	2	histology		RYEJ	0	6 m
Podnos (69)	2003	F	65	DCBD	2,2	biopsy during Ch-C		RYEJ	0	37 m
Volpe (70)	2003	M	19	PCBD	1	biopsy during Ch-C		RYEJ	0	12 m
El Rassi (71)	2004	F	41	LHD-H	4	histology		left hepatectomy + right HJ	0	240 m
El Rassi (71)	2004	M	79	DCBD	0,2	histology		PPPD	1	34 m
Menezes (72)	2004	M	30	CHD-CD	3	histology		RYEJ	0	18 m

Ligato (73)	2005	F	33	CHD	3,9	histology		RYEJ	0	10 m
Pithawala (74)	2005	F	38	CBD	5	biopsy during Ch-C		RYEJ	0	2 m
Hubert (75)	2005	F	46	CHD-CD	2,5	histology		RYEJ+Ch-C	0	102 m
Hubert (75)	2005	M	50	CD	0,4	biopsy during ERCP		RYEJ+Ch-C+ RFA for liver metastasis	1	
Nesi (14)	2006	M	30	DCBD	1,8	Preoperative (elevate blood serotonin level)		PPPD	0	84 m
Tzimas (76)	2006	F	29	LHD	2,8	histology		left hepatectomy + caudater lobe, right HJ	0	24 m
Kim (77)	2006	F	67	DCBD	1,6	histology		PPPD	0	10 m
Caglikulekci (78)	2006	F	40	CBD	0,7	biopsy during Ch-C		BDR	0	14 m
John (79)	2006	F	67	CBD		histology		PD	0	
Honda (80)	2006	M	76	DCBD	1,4	histology		PD	1	8 m
Ferrone (81)	2007	M	52	RHD-H	2,2	histology		Right Trisegmen-tectomy + BDR	0	
Sethi (82)	2007	M	51	PCBD	2,8	histology		RYEJ	0	22 m
Todoroci (83)	2007	M	73	DCBD	1,2	histology		PPPD	0	12 m
Colombo (84)	2007	M	52	CBD	2	histology		RYEJ	0	41 m
Stavridi (85)	2008	F	49	CD	1,4	histology		CH-C	0	12 m
Nafidi (86)	2008	F	31	CBD	1,2	histology		RYEJ	0	
Gusani (87)	2008	F	43	CHD	2,5	histology		RYEJ	0	132 m
Ferekouras (88)	2009	F	60	CD	2,1	histology		RYEJ+ STENT	1	112 m
Price (15)	2009	F	55	CHD-CD	0,6	gastrinoma		choledothomy, TR, T-tube + RFA liver metastasis	1	24 m
Price (15)	2009	F	33	DCBD		gastrinoma		PPPD	0	24 m
Tonnhofer (89)	2009	F	6	CHD		histology		RYEJ	0	24 m
Squillaci (90)	2010	M	70	CHD	4,5	biopsy during Ch-C		left hepatectomy + BDR, HJ	0	59 m
Zhan (91)	2010	M	10	DCBD	2	histology		PD	0	12 m
Cappell (92)	2011	M	42	DCBD	1,8	histology		PD	0	
Bhalla (93)	2012	F	28	CHD	2	histology		RYEJ	0	4 m
Linder (94)	2013	M	82	CBD	1,9	histology		PD	0	6 m
Yasuda (95)	2013	F	69	Hilar	2,5	histology		RYEJ	0	2y
De Luca (96)	2013	M	78	CBD	3	histology		PD	0	
Navas Cuellar (97)	2014	F	37	CBD	4	histology		RYEJ	0	
Yalav (98)	2014	M	16	CBD		histology		RYEJ	0	40 m
Sung Bae Park (99)	2014	F	75	CBD	2,7	histology		RYEJ	0	12 m
Safwan (9)	2016	F	41	CBD	2,8	Ga68DOTA-TATE			0	19 m
Hosoda (100)	2016	M	35	CBD	1,1	histology		RYEJ	0	
Sanchez-Cabùs (101)	2016	M	38	CBD	2	histology		RYEJ	0	
Brig (102)	2016	F	45	CBD	3,2	histology		PD	0	
Khan (103)	2016	M	64	CBD	1,3	histology		RYEJ	0	
Murakami (104)	2016	F	51	CBD	1,8	histology		RYEJ	0	
Abe (26)	2017	F	57	CBD	3	histology		RYEJ	0	34 m
Costin (105)	2017	F	37	CBD		histology		RYEJ	0	2y
Hoepfner (106)	2017	M	45	CBD	4	histology		RYEJ	0	6 m
Zhang (107)	2018	F	56	CBD	6	histology		RYEJ	0	8 m
Choi (25)	2019	F	33	CBD	2	citology brushing		RYEJ	0	10 m
Chaouch (108)	2019	M	39	CBD	2,4	histology		RYEJ	0	12 m
Umezaki (109)	2019	M	59	CBD	2,5	histology		RYEJ	0	11 m
Park (110)	2019	M	58	CBD	6,2	histology		RYEJ	0	12 m

Table 2:

	NET VB (n=95)
Gender (male)	37 (38.9%)
Age (years)	48 (± 17.3)
Location	
CBD tot	69 (62,1%)
-Proximal	11 (11,6%)
-Middle	33 (34,8%)
-Distal	15 (15,7%)
CHD tot	36 (37,9%)
-CHD only	13 (13,7%)
-Confluence 55	5 (5,3%)
-Cystic duct+ CHD	14 (14,7%)
-LHD/RHD+CHD	4 (4,2%)
Maximum diameter (cm)	2.2 (± 1.2)
Symptoms (main)	
Incidental finding	7 (7.5%)
Jaundice	61 (65.6%)
Abdominal pain	35 (37.6%)
Weight loss	16 (17.2%)
Cholelitiasis	13 (14%)
Nausea/vomiting	9 (9.7%)
Pruritus	5 (5.4%)
Diarrhea	5 (5.4%)
Weakness	5 (5.4%)
Time of diagnosis	
Histology	82 (86.3%)
NET	78 (95.1%)
Gastrinoma	4 (4.9%)
Preoperative	4 (4.2%)
Citology brushing	1 (25%)
Elevate 5-HT blood level	1 (25%)
Elevate 5-HIAA urine level	1 (25%)
Ga68DOTA-TATE	1 (25%)
Perioperative (biopsy during Cholecistectomy)	5 (5.3%)
Metastasis	
no	70 (73.7%)
nodal	17 (17.9%)
liver	9 (9.5%)
Treatment	
Biopsy	2 (2.2%)
Tumor resection	7 (7.5%)
BDR – RYEJ	55 (59.1%)
Pancreatoduodenectomy	17 (18.3%)
Hepatectomy	4 (4.3%)
Hepatectomy + BDR	6 (6.5%)
Cholecistectomy	3 (3.2%)
Cholecistectomy + TR	2 (2.2%)
OLT	2 (2.2%)
Immunohistopathology	
Cromogranin A +	74 (79.6%)
Sph +	27 (29%)
NSE +	22 (23.7%)
SF +	19 (20.4%)
Grimelius +	13 (14%)
Gastrin +	11 (11.8%)
Cytk +	10 (10.7%)
Serotonin +	9 (9.7%)
PP +	8 (8.6%)
Argentaf +	6 (6.5%)
SS +	5 (5.4%)
90-day mortality rate	1 (1.2%)
Mean follow-up (months)	33.3 (± 39.7)

NET: Neuroendocrine Tumors; 5-HT: 5-Hydroxytryptamine; 5-HIAA: 5-Hydroxyindoleacetic Acid; Ga68DOTA-TATE: Gallium-68 Ty3-Octreotate Dodecanetetraacetic Acid; BDR-RYEJ: Biliary Duct Resection – Roux-En-Y Hepaticojejunostomy; BDR: Biliary Duct Resection; Sph: Synaptophysin; NSE: Neuron-Specific Enolase; SF: Steroidogenic Factor-1; Cytk: Cytokeratin Immunohistochemistry; PP: Pancreatic Polypeptide; SS: Somatostatin Receptor.

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