Case Report

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Non-functioning neuroendocrine tumors of the common hepatic duct: a case report and literature review

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ABSTRACT

Extra-hepatic biliary tree neuroendocrine tumors are not common, accounting for about 0.1 % of all carcinoid tumors. Those affecting the common hepatic duct are very rare and their diagnosis is usually made post-operatively. Poorly differentiated tumors or neuroendocrine carcinomas are commonly seen in elderly, whereas well differentiated tumors, tend to occur in young patients, for whom surgery will lead to good long term results. About 100 cases have been reported in the English medical literature, showing good long term results after surgery for well differentiated (Grades 1 and 2) tumors. Herein, we report a case of an 18-year-old female, complaining from a dull epigastric pain related to a nodule compressing the common hepatic duct. After complete investigation, a laparotomy has been performed and showed a nodular tumor located in the common hepatic duct just above the insertion of the cystic duct with close contact with the pancreatic head distally. En bloc cholecystectomy with bile duct resection was performed and followed by a Roux-en-Y hepatico-jejunostomy. The pathology of the nodule came back to be a neuroendocrine tumor grade 2.

Keywords: Extrahepatic biliairy tract, Neuroendocrine tumors

INTRODUCTION

Neuroendocrine tumors (NET) are rare with 40 to 50 cases / million being reported per year. ^{1,2} They are slow-growing neoplasms representing 0.49% of all cancers and less than 2% of all gastro intestinal (GI) malignancies. Previously, these tumors were defined as "carcinoid tumors" but lately they are called NET. ³ Those located in the digestive tract are divided into either GI-NET or Pancreatic-NET (P-NET) with different pathogenesis, biology and response to treatment. ^{4,5} As for the Pancreatic-NET they can be either functional in 15% of cases or non-functional in the remaining 85%. Immunhistochemical staining is needed for diagnosis but not defining for classification. The occurrence of NET in

the extra-hepatic biliary tree is extremely rare as almost 100 cases were published in the English medical literature. Preoperative diagnosis was possible in few cases only. 6.7

The prognosis is based on the tumor grading on pathology. They are considered benign when dealing with well to moderately differentiated cells (Grades 1 and 2) and called NET. However, when poorly differentiated cells (Grade 3) are found, they are identified as neuroendocrine carcinomas (NEC). Specific data about extra pancreatic non GIT (ectopic pancreas) NET treatment is not available. But, surgery remains the only therapeutic option being a part of a multidisciplinary approach.

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CASE REPORT

An 18-year-old healthy girl consulted for a progressive dull epigastric non-irradiating pain with intermittent nausea without vomiting. She was complaining also from itching, early satiety, anorexia and fatigue. On physical examination, she looked slim, pale with subicteric sclera and poorly injected conjunctiva. The abdominal exam was normal. Laboratory tests have shown a cholestatic profile with increased total and direct bilirubin, high liver enzymes, but normal amylase and lipase in the serum. An abdominal ultrasound was done and did show dilated intra and extra hepatic bile ducts up to 14 mm in size, with a not well visualized gallbladder and a suspicious mass located in the common bile duct (CBD) of 32 x 22 mm of size above the pancreatic head with 2 small portal lymph nodes (LN). The ultrasound was followed by a magnetic resonance cholangiography (MRC) with showed a sclero-atrophic gallbladder with dilatation of both intra and extra hepatic bile ducts, a tiny retro pancreatic CBD and a 34 x 25 mm nodular and well circumscribed lesion located just below the liver hilum, compressing the CBD with close contact with the pancreatic head. Few celiac and hepatic LN were identified (Figure 1).

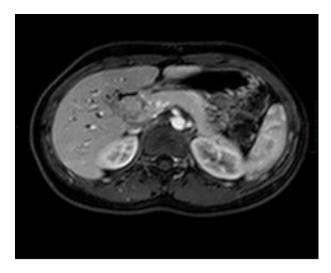


Figure 1: Cholangio MRI of a sclero-atrophic Gallbladder, a dilatation of both intra and extra hepatic Bile ducts, a tiny retro pancreatic common bile duct and a 34 x 25 mm nodular well circumscribed lesion, located just below the liver hilum with hyper signal in T2 with hypo signal in T1 and compressing the CBD with close contact with the pancreatic head and presence of few celiac and hepatic LNs.

To complete the investigation, an endoscopic ultrasound was performed which confirmed the previous findings showing a 20 mm CBD dilatation by a 4 cm hyperechoic mass compressing but not invading the portal vein with a homogeneous pancreas and absence of LN. Because of the difficulty to find if the lesion was intra or extra biliary, this test was completed by an endoscopic

retrograde cholangiopancreatography (ERCP) which confirmed the compressive nature of the tumor, most probably intrinsic because it was surrounded by the contrast material. The procedure was ended by the installation of a metallic stent (Figure 2).



Figure 2: Installation of a metallic stent in the common bile duct at the end of the ERCP procedure.

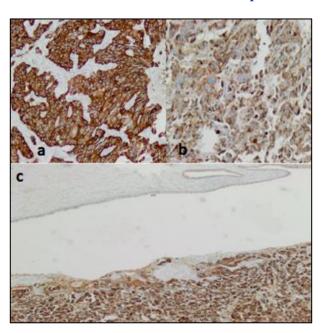


Figure 3: a) Cytokeratine positive; b) Chromogranine positive; c) Synaptophysine staining.

A decision for surgery was taken and the patient was operated under general anesthesia with a subcostal incision. The abdomen was free of ascitis and of any suspicious liver or peritoneal metastases. The dissection of the porta hepatis has shown an enlarged CBD with the presence of a well demarcated round 3 cm tumor extending from the upper limit of the pancreas distally to above the insertion of the cyst duct proximally. The common hepatic duct (CHD) was sectioned including the surrounding tissue at 1 cm distal to its bifurcation toward the upper limit of the pancreatic head followed by the complete extraction of the tumor and the surrounding tissue including the LN. Frozen sections of both the upper

and lower margins as well as the LN were done and they turned back to be free from any malignancy. The surgery was completed by a cholecystectomy with an end-to-side Roux in Y hepatico- jejunostomy. A drain was left in the Rutherford-Morrison fosse before the wound closure. The postoperative course was uneventful and the patient left the hospital on day 6. The histology and immunohistochemical staining of the tumor were in favor of a grade 2 neuroendocrine tumor compressing the CBD. Few pancreatic cells were found around the tumor without any vascular emboli or metastases in the gallbladder or the retrocholedocal and pericystic LN. As for the immunohistochemistry studies, the tumor was positive to Cytokeratine, Chomogranin A (CgA) and Synaptophysine staining (Figure 3).

DISCUSSION

Extra-Hepatic biliary tree neuroendocrine tumors (EHNET) are extremely rare and preoperative diagnosis is nearly impossible. 1.2.7 They account of 0.1 to 0.67% of all carcinoid tumors occurring most commonly in the CBD (Tables 1 and 2). 2.9

Like all NET, their behavior depends on their grading and their symptoms are caused by the tumor spread and growth. 10-12 Metastases occur mostly in the LN (43%) and the liver (32-73%) with a median survival around 2.2 years and a patient 5-year overall survival of 43%.¹³ In the past, classification of NET was based on tumor grading. In grade I (low) and grade II (intermediate), NET are considered well differentiated tumors, as for grade 3 (high), they are called poorly differentiated NEC.6-8 But recently, new European the Neuroendocrine/WHO nomenclature and classification for neuroendocrine tumors has included in addition to the grading system, the mitotic count and the Ki-67 index. 11

NET tend to occur in young patients (Table 1), and cases as young as 10-year-old patients have been published previously. In contradiction, NEC occurs most commonly in elderly patients and have a poor prognosis (Table 2). The CgA assay can be done in the tumor on pathology, urine and serum with a sensitivity of 74%. A high amount of CgA with normal levels of other hormones such as gastrin, insulin, and glucagon can be a sign of a non-functional pancreatic NET.

Table 1: Neuro-endocrine tumors of the extra-hepatic biliary tree, reported cases in the literature during the last 5 years.

| Case | Location | Size (mm) | Diagnosis | Surgery | Type | Age/sex | Morbidity |
|------------------------------------|-----------|--------------|---------------|-------------------|------|---------|-----------|
| Hosoda et al ¹ | CBD | 12 | Ct-scan ERCP | BDR + H-J | NET | 35/M | No |
| Yalav et al ¹⁴ | CBD | N/A | After surgery | BDR + H-J | NET | 16/M | No |
| Modlin et al ⁹ | CD | 8 | After surgery | BDR + H-J | NET | 51/M | No |
| Rykala et al ² | Hilar/CHD | 33 | After surgery | BDR + H-J | NET | 18 /M | No |
| Takahashi et al ¹⁵ | CBD | 30 | After surgery | Whipple procedure | NET | 28/F | No |
| Bhalla et a ¹⁶ | CHD | 20 | After surgery | BDR + H-J | NET | 28 / F | No |
| Cappelle et al ¹⁷ | CBD | 18 | After surgery | Whipple procedure | NET | 42 / M | No |
| Athanasopoulos et al ¹⁸ | Hilar/LHD | 3 | After surgery | PPPD | NET | 77 / M | No |
| Squillaci et al ¹⁹ | CHD | 20 | After surgery | BDR + H-J | NET | 52 / M | No |
| Nafidi et al ²⁰ | CHD | 45 | After surgery | BDR + H-J | NET | 70 / F | No |
| Nafidi et al ²⁰ | CBD | 16 | After surgery | BDR + H-J | NET | 31 / M | No |

 $CBD = Common \ Bile \ Duct; \ CHD = Common \ Hepatic \ Duct \ ; \ CD = Cystic \ Duct; \ LHD = Left \ Hepatic \ Duct \ ; \ BDR = Bile \ duct \ resection \ ; \ H-J = Hepaticojejunostomy \ ; \ NET = Neuroendocrine \ Tumor; \ PPPD = Pylorus \ Preserving \ Pancreaticodudenectomy; \ N/A = Not \ Available \ .$

In asymptomatic tumors, no extensive hormonal screening is justified. MRC is superior to CT-Scan for tumors less than 2 cm in size. In addition, it gives a complete mapping of the liver and the extrabiliairy tract as well, showing the tumor and its relation to the surrounding tissue.²⁴ A magnetic resonance angiography (MRA) can be added to MRC when vessels involvement is suspected.^{25,26}

Endoscopic ultrasound can be helpful in detecting tumor features as well as the presence of LN involvement and

regional tissue invasion.²⁷ Nuclear medicine imaging like Somatostatin receptor scintigraphy has the ability to scan the entire body to identify distant metastases.²⁸ It is considered the first line test with some limitations like missing small tumors (less than 1 cm of size) in 50% of cases and the lack of providing the exact tumor location unless associated to a CT Scan.^{9,24} However, Somatostatin receptor scintigraphy may be helpful in assessing the levels of somatostatin-receptor expression for therapy.²⁹ Gallium-68-DOTA-NOC (PET)/CT (octreoscan) has a sensitivity of 90 % and a specificity of

80% for metastases detection. Presently, it is considered a growing imaging modality of choice for all NETs in the United States.¹³

As for the management, there is no specific data concerning the extra pancreatic non GIT (ectopic pancreas) treatment, but surgery is still the only curative option combined to a multidisciplinary approach achieving a long post-operative disease free survival (DFS). 10,14,15,18

In the sporadic and locally advanced cases, no data support de-bulking surgery, but aggressive resection must be performed aiming for a R0 resection.³⁰

Circumferential invasion of either the portal vein with portal cavernoma or the superior mesenteric artery is considered a contraindication for surgery.³¹

As for the metastases resection, surgery is recommended only for G1 and G2 (well differentiated) tumors where more than 90% of the tumor burden must be removed. The aim of surgery is to prevent life-threatening and obstructive complications.³¹ Regarding liver metastases surgery, resection combined to ablative therapy and systemic treatment based on the location and the tumor resecability is indicated.³² However, liver transplantation has been offered as an alternative treatment for liver metastases in selected cases.³³

Table 2: Neuro-endocrine carcinomas of the extra-hepatic biliary tree, reported cases in the literature during the last 5 years.

| Case | Location | Size (mm) | Diagnosis | Surgery | Type | Age/sex | Morbidity |
|--------------------------|-----------------|-----------|------------------|-------------------|-------|---------|--------------------------------------|
| Samad et al ⁶ | Porta - hepatis | 47 | FNA | Autopsy | LNEC | 67/F | Died few months after the diagnosis |
| Park et al ⁸ | CBD | 27 | After surgery | BDR + H-J | NEC | 75/M | Died few months after the procedure |
| Hong et al ⁹ | CBD | 41 | N/A | BDR + H-J | NEC | 65/M | N/A |
| Hong et al ⁹ | CBD | 28 | N/A | Whipple procedure | SCNEC | 68/M | N/A |
| Hong et al ⁹ | CD | 23 | N/A | BDR and RH | LCNEC | 58/F | N/A |
| Hong et al ⁹ | CHD | 25 | N/A | BDR and LH | NEC | 71/F | N/A |
| Hong et al ⁹ | CBD | 30 | N/A | Whipple procedure | SCNEC | 71/F | N/A |
| Hong et al ⁹ | CHD | 17 | N/A | BDR+ H-J | NEC | 73/F | N/A |
| Hong et al ⁹ | CBD | 10 | N/A | Whipple procedure | SCNEC | 79/F | N/A |
| Lee et al ²² | CBD | 25 | After surgery | BDR + H-J | SCNEC | 59/M | Died 1 month following the procedure |

CBD = Common Bile Duct; CHD = Common Hepatic Duct; CD= Cystic Duct; LHD = Left Hepatic Duct; BDR = Bile duct resection; H-J = Hepaticojejunostomy; RH = Right Hepatectomy; LH = Left Hepatectomy; NEC = Neuroendocrine Carcinoma; SCNEC = Small Cell Neuroendocrine Carcinoma; LCNEC = Large Cell Neuroendocrine Carcinoma; N/A = Not Available.

Medical therapy is considered in advanced disease. Somatostatin analogues \pm Interferon is indicated in case of slowly progressive low proliferative P-NET (G1). Chemotherapy is given in P-NET (G2 and G3) and inoperable progressive liver metastases. Novel therapies, Everolimus and Sunitinib, are recently used with promising results. $^{10,35-37}$

No follow up for NET G1 tumors treated by radical resection is indicated. However, because of the high rate of recurrence, a strict follow up with CgA and CT/MRI is highly recommended on a yearly basis for NET G2 and every 6 months for NEC.¹⁰ Three review articles were found in the literature.^{7,19,38} In one of them, Michalopoulos et al stated that preoperative diagnosis was feasible in only 4 out of 78 cases reported from 1961

till 2012.7 During the last 5 years, about 21 new cases have been published in PubMed (Tables 1 and 2). Preoperative diagnosis is a must, since NET are mistakenly diagnosed as cholangiocarcinomas.³⁹ Despite advances in radiological techniques, the diagnosis remains subtle. In a retrospective study, some differ **EHNET** characteristics that from cholangiocarcinomas were identified.⁵ Adenocarcinomas occur most commonly in the upper 1/3 part of the CHD, whereas the EHNET are most commonly located in the CBD. In addition, periductal infiltrating type, a common growth feature for cholangiocarcinomas, is rarely seen in EHNET, which show an intraductal pattern of growth.⁵ All cases of NEC showed either vascular invasion or locally advanced growth. Finally, CT-scan of EHNET demonstrated a higher density when compared to the liver parenchyma on arterial phase. Some authorities have discussed the eventual role of gallstones in the pathogenesis of EHNET. However, in one review only 3 out of 50 patients with EHNET have had a history of gallstones disease. Some cases have been seen in the setting of choledochal cyst. One case was associated with a Hodgkin Lymphoma of the duodenum and another case was described in the setting of Von Hippel Lindau syndrome. Like all NET, surgery is the best treatment option and different strategies have been adopted according to the tumor location. Since CBD is the most common location of NET, bile duct resection with Hepaticojejunostomy is the most adopted surgery (Table 1). For patients with NEC, more extensive resections have been adopted (Table 2).

CONCLUSION

EHNET are extremely rare, and occur frequently in the CBD. Pre-operative diagnosis is crucial to eventually differentiate between benign tumors, cholangiocarcinomas and NEC. The management depends on NET WHO classification. Aggressive therapy should be applied in NEC.

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