# Klatskin Signet Ring Cell Neuroendocrine Tumor of the Biliary Tree

Eden Gerszman MD[1,4], Esther Kazlow MD[1,4], Victoria Vlasov MD[2,4], Dvir Froylich MD[1,4], Jacob Dickstein MD[3,4], Riad Haddad MD[1,4], and Ahmad Mahamid MD[1,4]

[1]Department of General Surgery, Carmel Medical Center, Haifa, Israel
[2]Department of Pathology Carmel Medical Center, Haifa, Israel
[3]Department of Gastroenterology, Carmel Medical Center, Haifa, Israel
[4]Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, Israel

**KEY WORDS:** Klatskin tumor, neuroendocrine carcinoma (NEC), neuroendocrine tumors (NETs), signet cell

*IMAJ* 2023; 25: 247–250

Neuroendocrine tumors (NETs) are a group of rare, heterogenous neoplasms that maintain unique morphologic and clinical features of neuroendocrine neoplasia and account for approximately 0.5% of all newly diagnosed malignancies. NETs are divided into two groups based on their histopathological morphology: well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). Well differentiated NETs are classified as G1, G2, or G3 based on their proliferation rate, whereas NECs are highly proliferative and poorly differentiated by definition [1]. Neuroendocrine neoplasms can occur almost anywhere in the body; however, they are most often seen in the gastrointestinal tract, pancreas, and lungs [2]. The extrahepatic bile duct is one of the rarest primary sites for NETs, accounting for 0.1% to 0.2% of NETs of the gastrointestinal tract [3]. Signet ring cell bile duct NETs are extremely uncommon and have no established incidence and prognosis due to their rarity. There is sparse information available regarding these tumors, and only a few cases have been reported in the literature to date. In this report, we presented the clinical course and surgical management of a 31-year-old female patient with a Klatskin signet ring cell NET.

## PATIENT DESCRIPTION

A 31-year-old female with a history of hepatic steatosis, presented to the hepatobiliary clinic with complaints of ongoing pruritus for several months. Her physical examination was unremarkable. Laboratory results revealed an elevation in hepatocellular and cholestatic enzymes (AST-49 U/L, ALT-64 U/L, GGT-255 IU/L). Bilirubin levels were within the normal reference range. Abdominal ultrasound did not reveal any abnormalities apart from fatty infiltration of the liver. Magnetic resonance imaging/magnetic resonance cholangiopancreatography showed a 4 × 3 × 3 cm lesion in the liver hilum causing mass effect on the distal common bile duct (CBD), narrowing of the right branch of the portal vein (with normal flow), and increased pressure on the hepatic artery without obstruction. The bile ducts were mildly dilated with greater distension in the right lobe of the liver in comparison to the left. This condition was likely due to the extra-biliary pressure of the mass on the CBD and confluence. A nonspecific 1.4 × 3.2 cm lymph node was seen in the porta hepatis. An ultrasound-guided biopsy was performed with a histopathological differential diagnosis that appeared somewhere between an intraductal papillary neoplasm of the bile duct and a neuroendocrine tumor. A $^{18}$F-fluorodeoxyglucose positron-emission tomography/computed tomography (PET/CT) scan showed high pathological intake in the liver hilum with portocaval involvement.

Considering these findings, and because of an unclear solid liver hilum mass causing extra-biliary pressure on the CBD rather than biliary tract mass, a repeat ultrasound-guided biopsy was performed. Pathology reported cores of hepatic tissue that were infiltrated by a malignant tumor. The tumor was immunohistochemically and morphologically prototypical of a neuroendocrine tumor type, which was further classified as grade 1 with the potential to have been of metastatic origin. A DOTATATE PET/CT scan was performed, which showed high intake in

the liver hilum and segment four of the liver. This result is highly characteristic for NETs. No other pathological intake was seen. Endoscopic ultrasound was conducted to search for primary pancreatic NET lesions and showed the common bile duct and pancreatic duct to be within normal range. Mild thickening of the gallbladder wall was seen without evidence of gallstones. The papilla of Vater was endoscopically normal. The established mass in the porta hepatis was seen without focal pancreatic lesions present, and therefore a pancreatic biopsy was not taken. The diagnosis of a peri-hilar mass presenting with NET characteristics was established. Gastroscopy and colonoscopy were performed in search of a primary digestive system NET. Gastroscopy revealed mild gastritis without malignancy, and the colonoscopy was normal. Chromogranin A level was 36 ng/ml and urine 5-HIAA level was 3.74 mg over 24 hours. During a multi-disciplinary discussion with the hospital tumor board, a decision was made to proceed with surgery.

A robotic-assisted surgery exploration was performed. During the surgery, fatty infiltration of the liver with a 4 × 3 cm mass at the level of porta hepatis was seen. Intra-operative ultrasound revealed no liver or peritoneal metastases. The lesion originated from the bile duct bifurcation, continued 3 cm distally to the common hepatic duct, and culminated to involve the right hepatic duct into the right lobe of the liver and the distal left hepatic duct [Figure 1]. Lymph nodes in the porta hepatis were enlarged and a frozen section could not rule out metastatic NET. Conversion to open surgery was performed because of difficulties in surgical progression due to difficult anatomy. The patient underwent right hepatectomy with left hepaticojejunostomy and extensive lymph node dissection of the porta hepatis. The patient recuperated well with no post-operative complications. She was discharged 10 days after the surgery.

The final pathology report revealed that surgical margins were free of tumor. The tumor was found 2.5 cm from the distal bile duct surgical margin and 1.7 cm from the liver surgical margin. Macroscopically, two tan/red tumor nodules were located at the liver hilum, measuring up to 4.5 cm at its largest diameter. The tumor extended into the right and left bile ducts. Microscopically, the tumor was mostly delimited by a fibrous pseudocapsule and showed solid sheets, ribbons, and thick anastomosing cords with hyperchromatic and finely stippled chromatin. No conspicuous nucleoli were found. A mild to moderate pleomorphism was seen. Areas demonstrating cells with vacuolar cytoplasm and eccentric hyperchromatic nuclei compressed to the periphery of the cells was seen within the tumor itself. This finding confirmed a so-called *signet ring* cell pattern. Immunohistochemically, the tumor cells were positive for pan-keratin and for the following neuroendocrine markers: synaptophysin, chromogranin, and CD56. On average, less than 1 mitotic figure per 10 high power field was counted. The Ki67 marker of proliferation was low (2%). The diagnosis of NET grade 1, with areas showing a signet ring cell morphology, was established [Figure 1]. Five lymph nodes were tested, all were tumor free. Over the course of 8 months post-surgery, the patient continued oncological follow-up with DOTATATE PET/CT, chromogranin A, and urine 5-HIAA level monitoring, without any pathological uptake seen. The results indicated a lack of recurrence in the absence of active oncological treatment.

## COMMENT

The World Health Organization classifies NETs as neoplasms of neuroendocrine cell origin with neuroendocrine characteristics. Neuroendocrine tumors are further sub-classified into NET grade 1, NET grade 2, NET grade 3, and NEC. The most common NETs are those that arise within the gastropancreatic system, which constitutes approximately 73.7% of all cases. This number is followed by trachea-bronchial-pulmonary NETs, which constitute approximately 25.1% of cases. In contrast, extrahepatic bile duct NETs account for only 0.32% of all primary NET sites, and 0.19% are subclassified as NECs [2,4].

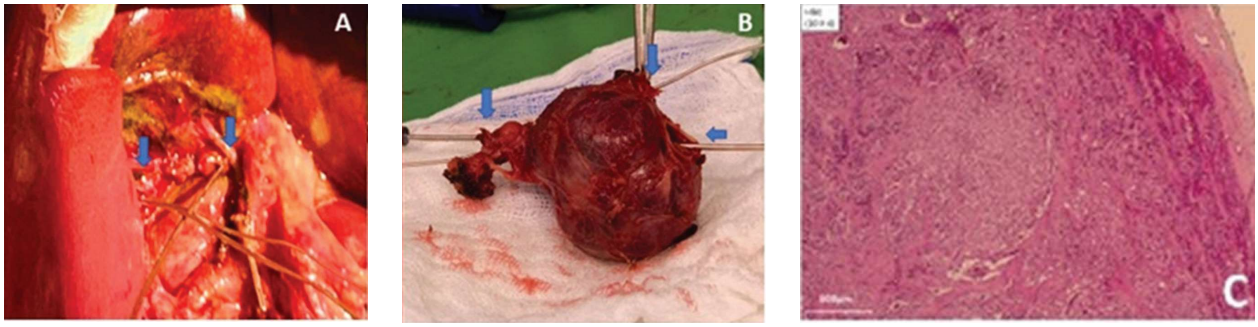
In a 2019 literature review of hilar bile duct NETs, 25 case reports revealed the median age at onset as 37 years. Approximately 68% of these patients were female, and the most common initial presenting symptom was jaundice. Furthermore, the tumor was predominantly located in the common bile duct, followed by the common hepatic duct bifurcation [3]. It is important to note that these are cases of bile duct NETs without signet ring cell morphology. These specific types of tumors are rare and hardly reported; therefore, the prognosis is unclear. Our patient was a 31-year-old female, consistent with the demographics presented. In addition, NET involvement of other organs was not found, which suggested that the patient's biliary tumor was of primary origin rather than a metastatic disease from another more common NET site. Even though preoperative diagnosis did not show a bile duct tumor, a mass in the liver

**Figure 1.** Showing macroscopic and microscopic view of the specimen

**[A]** Dissection and resection of the extrahepatic biliary tree. Vertical arrows: right and left hepatic ducts

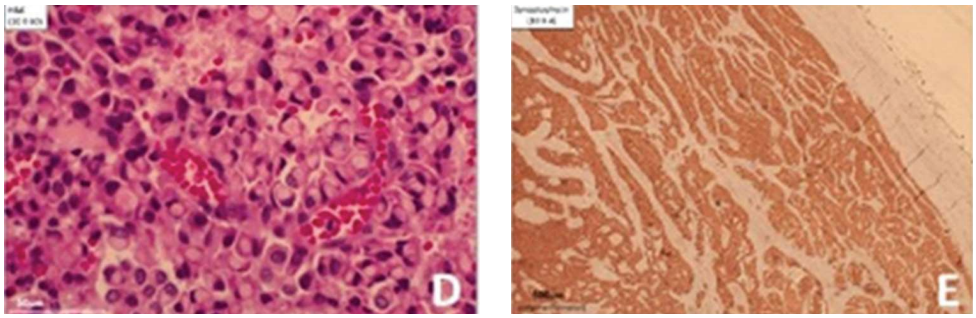
**[B]** The resected specimen; vertical arrows: right and left hepatic ducts; horizonal arrow: common hepatic duct

**[C]** A low microscopic magnification (10 × 4) of the tumor stained by hematoxylin and eosin (H&E), showing a segment of the tumor that is composed of solid sheets and cords, demarcated by a fibrous pseudocapsule (on the left)




**[D]** A high microscopic magnification (10 × 60) of the tumor, stained by hematoxylin and eosin (H&E) showing an area composed of sheets of signet ring cells

**[E]** A low microscopic magnification (10 × 4) of the tumor, expressing a strong positivity for the synaptophysin immunohistochemical marker reflecting neuroendocrine differentiation




hilum causing narrowing of the bile ducts was seen during the surgery, consistent with the location reported in the literature review.

To date, most treatment recommendations come from small case series, thereby making the optimal treatment for such patients open for discussion. In the absence of optimal treatment guidelines, options vary between R0 surgery for resectable tumors to systemic therapy or multi-visceral transplantation for unresectable and metastatic tumors. Surgical options include extrahepatic bile duct resection and reconstruction, Whipple procedure for distal CBD tumors, and hepatectomy for tumors involving the hilar bile ducts. Liver transplantation for unresectable tumors was performed in several cases, although there are no comprehensive guidelines or indications for this method of treatment [3].

Due to the rarity of signet ring cell bile duct NETs, there is no established prognosis in the literature. However, a closely related comparative study of 221 cases of carcinoid tumors and small-cell carcinomas of the gallbladder and extrahepatic bile ducts reported 5- and 10-year survival as 80% and 84%, respectively. In that study, 10% of carcinoids of the extrahepatic biliary system were associated with additional tumors either as first or second primaries [4].

There are several adjuvant therapies available today for the treatment of extrahepatic bile duct NETs including somatostatin analogs, peptide receptor radionuclide therapy with radiolabeled somatostatin analogs, targeted therapy such as sunitinib and everolimus, interferon alpha, chemotherapy, and interventional radiology such as radiofrequency ablation or embolization in selected cases [5]. In

our patient, no adjuvant treatment was given because the tumor was fully resected with R0 margins, and no residual disease was seen on follow-up imaging. The patient was doing well with no recurrence seen during oncological follow-ups.

## CONCLUSIONS

Extrahepatic bile duct NETs are rare, and among this group of tumors, signet ring cell bile duct NETs are even more uncommon. Preoperative diagnosis of bile duct NETs are difficult to establish due to their complicated location, histology, and the rarity of this specific type of tumor in the bile ducts. Surgery may be the optimal treatment, although there is a significant amount of progress with molecular targeted therapy. Variable treatment options are available including multi-modality therapy. In the absence of universally accepted guidelines, individual treatment planning should be conducted in conjunction with multidisciplinary collaboration and a national NET registry initiation.

**Correspondence**

**Dr. E. Gerszman**
Dept. of General Surgery, Carmel Medical Center, Haifa 3436212, Israel
**Phone:** (972-4) 825-0292
**Fax:** (972-4) 825-0927
**Email:** eden.gerszman@gmail.com

**References**

1. Rindi G, Mete O, Uccella S, et al. Overview of the 2022 WHO classification of neuroendocrine neoplasms [Review]. *Endocr Pathol* 2022; 33 (1): 115-54.
2. Modlin IM, Sandor A. An analysis of 8305 cases of carcinoid tumors. *Cancer* 1997; 79 (4): 813-29.
3. Umezaki N, Hashimoto D, Yamashita Y-I, et al. Neuroendocrine tumor of the hilar bile duct [Review]. *Anticancer Res* 2019; 39 (2): 903-7.
4. Albores-Saavedra J, Batich K, Hossain S, Henson DE, Schwartz AM. Carcinoid tumors and small-cell carcinomas of the gallbladder and extrahepatic bile ducts: a comparative study based on 221 cases from the Surveillance, Epidemiology, and End Results Program. *Ann Diagn Pathol* 2009; 13 (6): 378-83.
5. Zandee WT, de Herder WW. The evolution of neuroendocrine tumor treatment reflected by ENETS guidelines [Review]. *Neuroendocrinology* 2018; 106 (4): 357-65.

Capsule

## Neat regulation of macrophage function

Nuclear paraspeckles, a type of membraneless organelle comprising molecular condensates of protein and RNA, may regulate how macrophages respond to infection. **Azam** and colleagues used microscopy to follow the dynamics of nuclear paraspeckles in macrophage cell lines responding to signs of infection in vitro. The paraspeckles formed quickly after stimulation but disassembled after 2 hours in a process that required degradation of one paraspeckle component, the long noncoding RNA of *Neat1*. Murine macrophages deficient in *Neat1* were impaired in their ability to produce proinflammatory cytokines and antimicrobial molecules, which was correlated with a decreased ability to control the replication of intracellular pathogens on infection of the cells.

*Proc Natl Acad Sci USA* 2024; 121 (9): e2312587121
Eitan Israeli

Capsule

## A gut microbial signature for combination immune checkpoint blockade across cancer types

**Gunjur** and colleagues performed deep shotgun metagenomic sequencing of baseline fecal samples from a unique, richly annotated phase 2 trial cohort of patients with diverse rare cancers treated with combination ICB (n=106 discovery cohort). The authors demonstrated that strain-resolved microbial abundances improve machine learning predictions of ICB response and 12-month progression-free survival relative to models built using species-rank quantifications or comprehensive pretreatment clinical factors. Through a meta-analysis of gut metagenomes from a further six comparable studies (n=364 validation cohort), they found cross-cancer (and cross-country) validity of strain–response signatures, but only when the training and test cohorts used concordant ICB regimens (anti-PD-1 monotherapy or combination anti-PD-1 plus anti-CTLA-4). This finding suggests that future development of gut microbiome diagnostics or therapeutics should be tailored according to ICB treatment regimen rather than according to cancer type.

*Nature Med* 2024; 30: 797
Eitan Israeli