

## Case Report

# Silent neuroendocrine tumor of biliary confluence

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## ABSTRACT

Neuroendocrine tumors (NETs) of the extrahepatic bile ducts are extremely rare. They are heterogeneous entities of varied histopathological features. The pathological types vary greatly with regards to biological behavior and prognosis. We presented such a case of silent tumor of the biliary tract of neuroendocrine origin in a middle-aged female with nonspecific abdominal pain without any clinically obvious signs which on radiological imaging revealed a tumor of hepatic confluence with metastatic deposits in liver for which she underwent left trisectionectomy with segment 7 metastatectomy. As per the literature reviews regarding extrahepatic bile duct NET these tumors are more common in the middle age population with a female preponderance. The tumors were symptomatic in majority of patients and the symptoms are mostly related to tumor mass and its invasion of adjacent structures or metastases rather than hormone and vasoactive peptide secretions. The low incidence and uncommon modes of presentation makes the diagnosis tough and management challenging.

**Keywords:** Neuro endocrine tumor, Extra hepatic biliary tree, Hilar confluence, Trisectionectomy, Metastatectomy

## INTRODUCTION

Neuroendocrine tumors (NETs) of the extrahepatic bile ducts are extremely rare.<sup>1</sup> Since Pilz first described it in 1961, only less than 200 cases have been described so far. We have seen an increase in their incidence (3.65 /100.000/year) in recent years.<sup>2</sup>

The most frequent sites of extrahepatic biliary NETs are the common hepatic duct and the distal common bile duct (19.2%), followed by the middle of the common bile duct (17.9%), the cystic duct (16.7%), and the proximal common bile duct (11.5%).<sup>3</sup> They are an extremely heterogeneous entity of varied histopathological features whose pathological types vary greatly with regards to biological behavior and prognosis.<sup>4</sup>

The WHO classification 2000 is widely used to categorize NETs for all anatomical sites.<sup>5</sup> Neuroendocrine tumors can

be divided into functional and non-functional based on their clinical features and are classified as localized, regional and metastatic tumors with regards to staging. As cholangiocarcinoma accounts for about 80% of all primary biliary tumors, it is important to think about other options despite their low frequency when patient presents with abnormal characteristics.<sup>3</sup>

The most sensitive immunohistochemical markers are expression of neuron-specific enolase, synaptophysin and chromogranin A. Chromogranin A is elevated in 90% of neuroendocrine tumors and therefore can be an effective biological marker for preoperative diagnosis.

Biliary neuroendocrine tumors remain silent until they metastasize or invade neighboring organs. The rarity of condition, uncommon modes of presentation and absence of serum markers make the diagnosis tough and management challenging.<sup>6</sup>

## CASE REPORT

57-year-old lady without any comorbidities with previous history of open cholecystectomy 20 years back presented with chief complaints of mild heaviness and bloating sensation after meals for 6 months with no previous history of jaundice/ itching/ weight loss/ loss of appetite.

Three years back she was incidentally detected to have mild dilatation of intrahepatic biliary radicles. As she was asymptomatic, she did not get further evaluation done despite being advised. She presented to the OPD with yellowish discoloration of sclerae.

On clinical examination she was icteric and the systemic assessment was normal. The routine blood investigations were normal and LFT revealed marginal elevation of alkaline phosphatase (ALP-138) gamma-glutamyl transpeptidase (GGT-95) and serum bilirubin (t. bil-3.2).

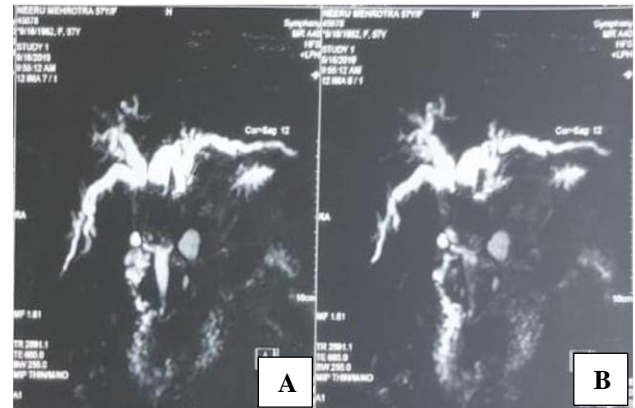
Repeat USG showed dilated intrahepatic biliary radicles (IHBR) and common bile duct (CBD). Magnetic resonance cholangiopancreatography (MRCP) revealed a lobulated mass lesion at the hilum extending into the left ductal system and infiltrating into the right anterior sectoral duct with a large nodal mass along the hepatoduodenal ligament closely abutting the head of pancreas with resulting mass effect and obstructive biliopathy (Figure 1). Endoscopic ultrasound (EUS) and biopsy revealed hilar mass with large vascular peripancreatic nodal mass and EUS guided biopsy was suggestive of grade 2 metastatic NET with MIB labelling index 3%. Serum chromogranin and alpha-fetoprotein (AFP) were normal.

DOTA PET revealed dotatate avid soft tissue mass lesion in biliary confluence extending into proximal CBD with luminal compromise and upstream dilatation of bilateral intrahepatic biliary radicles with dota avid enlarged nodes in periportal and portocaval locations with hepatomegaly and dota avid hypodense lesions in segment 3, 6, 7 and 8 (Figure 2 and 3).

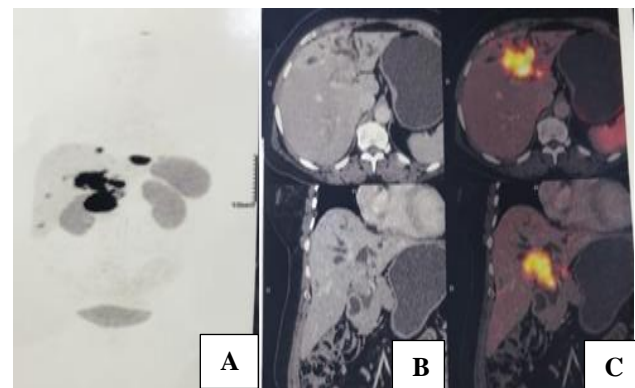
She underwent open left trisectionectomy with portal lymphadenectomy with segment 7 metastatectomy with roux en y hepaticojejunostomy to right posterior sectoral duct (Figure 4 and 5). Intra-operatively there was no ascites or peritoneal metastasis, there was a firm to hard growth at confluence with adjacent desmoplastic reaction with surface nodules over segment 3, 5, 7 and 8 with enlarged periportal nodes, largest measuring 4.5×3 cm with right lobe hypertrophy and left lobe atrophy. Intra operative USG (IOUS) revealed no lesion in segment 6. The intra-operative frozen section distal CBD and Proximal right posterior sectoral duct were found to be negative.

Histopathology revealed well differentiated NET grade 2, of left hepatic duct, confluence, common hepatic duct, right anterior sectoral duct with focal areas of necrosis and

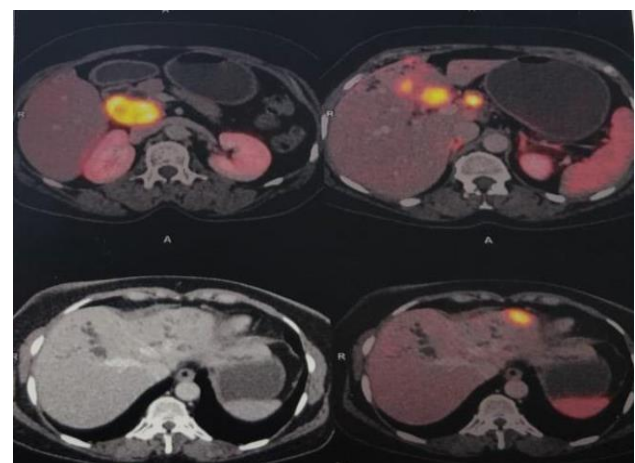
tumor invading beyond the wall of bile duct into the adjacent soft tissue and liver parenchyma with negative proximal and distal margins. 3 out of the 19 lymph nodes were found to be involved with no extra nodal extension. In immunohistochemistry the tumour showed diffuse positivity for synaptophysin/ chromogranin/CD 56 and Ki index 8-10%.



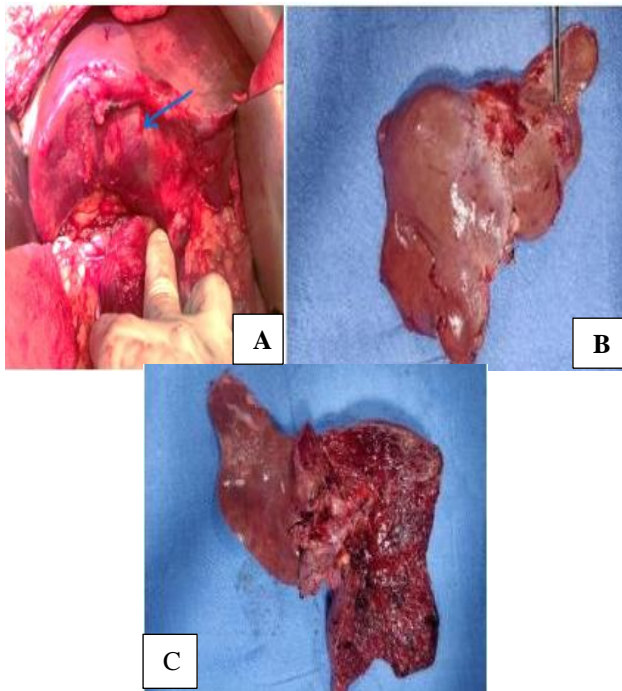
**Figure 1 (A & B): MRCP showing dilated CBD and dilated IHBR.**



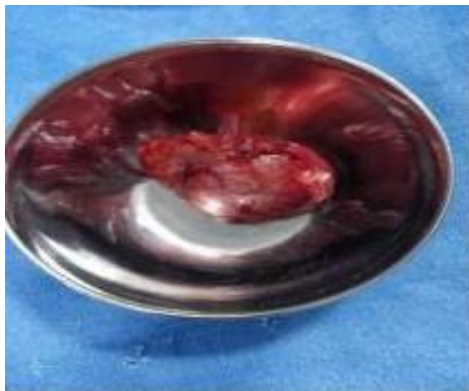
**Figure 2 (A-C): DOTA-PET showing the hepatic metastatic deposit.**



**Figure 3: PET-CT showing the metastatic HDL node.**



**Figure 4: (A) Intra-operative finding; (B) resected left tri segmentectomy with segment 6 metastatectomy specimen; and (C) trisegmentectomy specimen.**



**Figure 5: Enucleation of node.**

## DISCUSSION

Majority (80%) of the tumors arising from the extrahepatic bile ducts are well-differentiated adenocarcinomas. Primary neuroendocrine tumors of the extrahepatic biliary tree are exceedingly rare.<sup>7</sup> The most common site for NETs is the gastrointestinal tissues accounting for approximately 75 percent of all cases.<sup>8</sup> The incidence of NET in biliary system accounts for just 0.2-2.0% of tumors because there are no neuroendocrine cells in the extrahepatic bile duct mucosa.<sup>9</sup> For extrahepatic bile duct NET, the common hepatic duct and distal CBD are sites of predilection (accounting for 19.2% of bile duct tumors); the middle of the CBD accounts for 17.9% of tumors, the cystic gall duct accounts for 16.7%, and the proximal CBD accounts for 11.5%.<sup>10,11</sup> NETs are composed of

multipotent cells having the ability to secrete numerous hormonal substances and vasoactive peptides, with serotonin, gastrin, somatostatin, vasoactive intestinal polypeptide, glucagon, and insulin being the most common. However, extrahepatic bile duct NETs rarely induce symptoms associated with these hormones and/or polypeptide secretion.<sup>12</sup>

The etiology of bile duct NETs remains unclear. Certain studies point that NETs are linked with cholelithiasis and congenital malformation of the biliary tract, both of which lead to chronic inflammation which in turn leads to metaplasia of bile duct epithelial cells and then metaplasia into NET.<sup>13</sup> According to previous literature, cholangiocarcinoma is often the most common tumor to be diagnosed in the bile duct.<sup>14,15</sup> Pathologically cholangiocarcinoma behaves like adenocarcinomas and common bile duct NETs are extremely rare. Immunohistochemistry determines the degree of differentiation of the NETs. NET can be divided into three grades (G1-G3), according to the number of mitotic images and the Ki-67 index.<sup>16</sup>

As per the literature review regarding extrahepatic bile duct NET by Nickos et al 47 years is the median age of presentation (range: 6-79 years), with a female (61.5%) preponderance.<sup>17</sup> The tumors are symptomatic in 88.5% of patients and the symptoms were mostly related to tumor mass growth, invasion of adjacent structures or metastases rather than hormone and vasoactive peptide secretion. With jaundice (60.3%) being the most common symptom of presentation and pruritus (19.2%) and only 9% hormone and vasoactive peptide-related symptoms. About one-third of patients with extrahepatic bile duct NET present with metastases with involvement of the local lymph nodes (19.23%) or to the liver (16.7%), Unlike carcinoma of the extrahepatic bile duct wherein two-thirds of patients present with metastatic disease, our patient presented initially with no symptoms and only after development of jaundice after 3 years was evaluated further. With the help of a base line MRCP a diagnosis of an obstructed lesion of the extrahepatic biliary tree was established and the ERCP guided FNAC provided the tissue diagnosis with normal serum biochemistry and the chromogranin A levels were deceptively normal.

NETs are complex diseases and are an example of how a multidisciplinary approach has a favorable impact on diagnosis, treatment and control. Surgical radical resection is the main treatment for NETs of biliary tract origin. The operation is classified into three types according to the position of the mass: pancreaticoduodenectomy (tumor located in the distal CBD), bile duct resection, and cholangiojejunostomy (tumor located in the middle CBD), combined with partial hepatectomy for patients who have liver metastases. Lymph node dissection is advocated, but there is no uniform standard for the extent of specific dissection. The tumor in our case was located at the confluence with intense desmoplastic reactions and was associated with infiltration into the right anterior sectoral



duct with a large nodal mass extending along the hepatoduodenal ligament that warranted a radical surgery in the form of Open left trisectionectomy with portal lymphadenectomy with segment 7 metastatectomy with roux en y hepaticojejunostomy to right posterior sectoral duct. In case of liver multifocal lesions, chemoembolization constitutes the best treatment; but if metastases are confined to one of the two hepatic lobes may be taken into account the removal of one or more liver segments. Preoperative imaging in the form of DOTA PET revealed Dota avid hypodense lesions in segment 3, 6, 7 and 8 in our case but the intra operative ultrasound revealed no lesion in the segment 6.

Extrahepatic bile duct NETs slowly grow, and aggressive surgical resection is considered to be the only curative treatment.<sup>18</sup> Even in palliative resection cases, medical treatment, including systemic chemotherapies, targeted therapies, somatostatin analogs, liver-directed therapies, such as chemoembolization or thermoablation and peptide receptor radionuclide therapy, may sometimes achieve disease control.<sup>18</sup> However, these are treatment strategies for gastro-entero-pancreatic NETs and not for extrahepatic bile duct NETs because of their rarity.

Regarding debulking, we can use it for functional neoplasia, in order to reduce the amount of secreting tissue and then to control the symptoms of the disease, ensuring the patient a better quality of life but not a longer survival.<sup>19,20</sup> Among the possible complications are: haemorrhage, both intra-op and in the first 24-48 postoperative hours; liver failure, if major hepatic resections are performed, leaving insufficient residual liver to maintain its normal functions, then we might have jaundice or ascites; biliary fistulas; sepsis, and then fever or hypothermia, rapid breathing, fast heart rate, confusion, edema, up to the shock.<sup>21</sup>

## CONCLUSION

Despite the recent advances there are no uniform guidelines for NET treatment, especially for radiotherapy and chemoradiotherapy postoperatively. It is therefore important to report this tumor due to its uncommon nature.

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