



Case Report

A Unique Case of Metastatic Recurrent Neuroendocrine Tumor in a Transplanted Liver Patient with Initial Diagnosis of Primary Well-Differentiated Intrahepatic Biliary Neuroendocrine Tumor

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Abstract

Neuroendocrine tumors (NET) of biliary ducts are very rare, accounting for only 0.2-2% of all gastro-entero-pancreatic neuroendocrine tumors GEP NETs [1]. More specifically, intrahepatic biliary neuroendocrine tumors are excessively rare, with few cases reported in medical literature so far. We present a very unusual case of a primary intra-biliary well differentiated NET, treated initially with SSA agents, Chemotherapy and liver directed procedures. Subsequently, the patient underwent liver transplant for liver-isolated disease. Unfortunately, two years later developed tumour recurrence in the liver as well as distant metastases involving the bone and adrenal gland, which were re-treated with SSA agent, re-challenge chemotherapy, and repeated liver directed therapies. The patient continues to have a favourable clinical course, currently awaiting systemic therapy with Lu177-Dotatate treatment.

Introduction

Neuroendocrine tumors (NETs) of biliary ducts are very rare, accounting for only 0.2-2% of all gastro-entero-pancreatic neuroendocrine tumors GEP-NETs [1]. Specifically, intrahepatic biliary neuroendocrine tumors are excessively rare. These tumors are nearly impossible to be differentiated from cholangiocarcinoma prior to biopsy or surgical resection, however they have incomparably far better prognosis. Approximately one-third of patients have metastatic disease at the time of diagnosis [2] with liver being the most common metastatic site.

[4] Neuroendocrine tumors are presumably originating from enterochromaffin cells, which are found in gastro-entero-pancreatic tract (GEP NET), but very unusually in the biliary tract, due to scant population of these cells in biliary ducts. Presumably, these cells are affected by pre-malignant metaplasia, hence the origin of uncommon NET occurrence [6]. This is why primary biliary neuroendocrine tumors are exceedingly rare [5]. The most common symptoms prompting investigations leading to the diagnosis, are jaundice (60.3%), pruritus (19.2%), cholelithiasis co-existence (19.2%) and less commonly hormone-related and vasoactive-related symptoms (9%) [7]. According to WHO

classification and grading (2010), all neuroendocrine neoplasms are categorized into neuroendocrine tumors, NET (low or intermediate grade, G1-G2 NETs, Ki67 < 20%), a subtype of high-grade G3 NETs with Ki67>20% and neuroendocrine carcinomas NEC (Ki67 > 20 %) [8]. The strongest factors influencing patient's prognosis are histological differentiation, tumor grade, mitotic activity, and presence of metastasis. [8].

The only potential curative treatment for NETs is surgical resection [3]. Other treatment options for metastatic hepatobiliary NETs include multiple modalities: somatostatin analogues, systemic therapy (cytotoxic chemotherapy, molecular agents, radionuclide based therapy), liver directed therapies and orthotopic liver transplantation in selected patients. More specifically, the initial therapeutic option for patients with isolated simple or complex liver metastasis without evidence of disease progression elsewhere, is surgical resection with potential addition of ablative techniques. However, in the setting of diffuse liver metastasis, alternatives of treatment include somatostatin analogues, chemotherapy, peptide receptor radionuclide therapy, liver embolization procedures (TARE) and potentially liver transplantation in selected patients [9]. Indications for liver transplantation in patients with metastatic NET (liver metastases only) are: 1) life-threatening treatment-refractory hormonal disturbances, 2) large tumor bulk, 3) disease not amenable to surgical resection in the absence of extrahepatic disease, 4) high Ki67 index (> 20%) and 5) patient's poor performance status [10,11].

We present a unique case of recurrent NET in the transplanted liver of a patient previously diagnosed with intrahepatic biliary NET, post hepatectomy and orthotopic liver transplant. Below is the unusual case of a 46-year-old female diagnosed with primary intrahepatic biliary NET involving liver metastasis, successfully treated with somatostatin analogues, chemotherapy and trans arterial liver embolization, followed by successful liver transplantation, who unfortunately experienced metastatic NET recurrence in the transplanted liver.

Case Presentation

46-year-old-female with no significant past medical history, presented with a few months of postprandial abdominal pain and diarrhea, and was found to have multiple lesions in the right liver lobe. Laboratory results were negative for hyperbilirubinemia and her ALT/AST remained within normal limits. Percutaneous ultrasound-guided liver lesion biopsy revealed well-differentiated, G1 neuroendocrine tumour with acinar features and Ki67< 5%. An extensive workup in search of primary site was done, with no positive results. Both anatomic and functional imaging confirmed that her entire disease was confined to the liver (Figure 1,2).

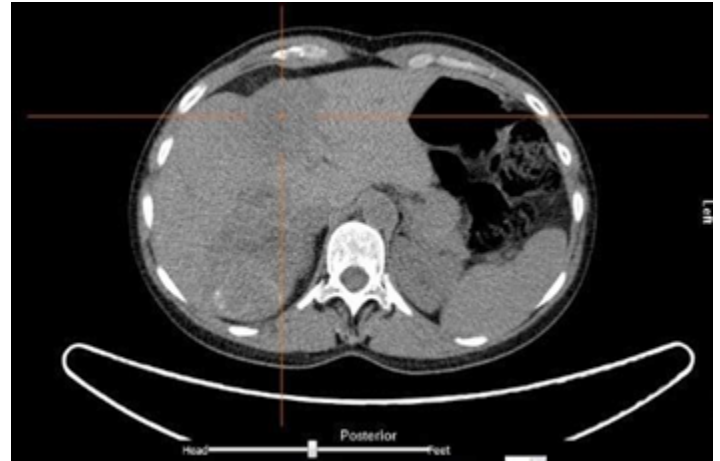


Figure 1: CT scan revealing multiple heterogeneous hepatic lesions with peripheral arterial enhancement.

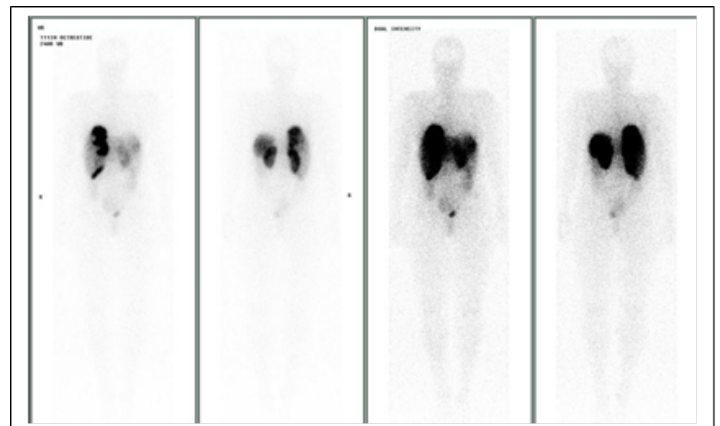


Figure 2: Octreotide scan showing three dominant liver lesions in segment VII/V, segment VI/VII and segment IVb.

The patient was treated as well-differentiated G1-GEP-NET based on histology and was placed on long-term therapy with long-acting somatostatin analogue. She also received 19 cycles of chemotherapy with capecitabine and temozolomide (CAPTEM). Concurrently, local therapies were also offered to address some the largest liver lesions. Initially, she underwent two trans-arterial radioembolizations (TARE) of multiple metastatic lesions in the right liver lobe with Y-90, followed by bland embolization of the left sided hepatic artery. After numerous cycles of CAPTEM, she developed bone marrow suppression, due to cumulative chemo toxicity. Therefore, CAPTEM therapy was interrupted, and the patient remained on SSA alone for the following 3 years, with no evidence of disease progression.

A repeat liver biopsy completed post treatment, confirmed presence of well-differentiated neuroendocrine tumour of

intrahepatic biliary origin, after an enhanced pathology review. This represents a rare variant. Again, there was no evidence of extrahepatic disease or metastasis on imaging. Based on the above, she was enlisted for liver transplant. She underwent total hepatectomy followed by orthotopic liver transplant. Intraoperatively, it was discovered that the tumour was adherent to the diaphragm, adrenal gland, and retro peritoneum. Despite this, hepatectomy was performed successfully without any spillage of the tumour, followed by liver transplantation. Immunosuppressive therapy with Tacrolimus was initiated post-operatively and the patient was placed on oncological surveillance.

Nearly two years following liver transplantation, a routine Ga-68 PET scan showed multiple DOTATATE avid hepatic and bone metastasis, as well as left adrenal gland involvement, consistent with recurrent liver disease as well as new distant metastasis (Figure 3).

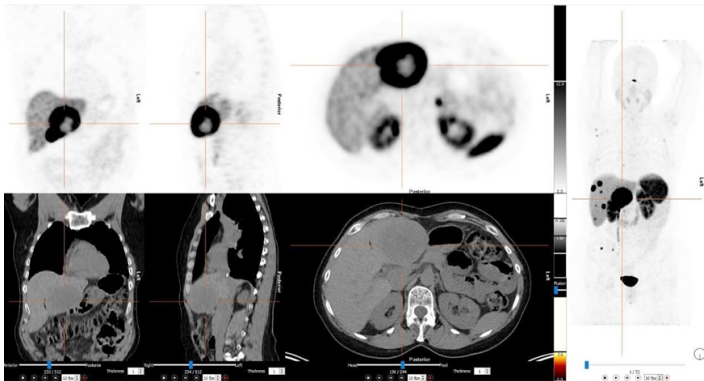


Figure 3: Gallium scan revealing multiple DOTATATE avid hepatic metastases with the largest one in the left liver lobe.

This prompted another liver biopsy, that confirmed recurrence of intra-hepatic neuroendocrine tumor. However, the biopsied liver lesion had high aggressive features with higher histologic grade (Ki67 >75%), in keeping with NEC. This lesion is illustrated in FDG PET images below. By this time, the histologic picture was consistent with a de-differentiated NET, composed of an aggressive NEC component within the background of previously known low grade well-differentiated NET.

Therapy with octreotide was re-initiated first. Then, due to increasing disease volume in the transplanted liver, re-challenge CAPTEM chemotherapy (capecitabine and temozolomide) was introduced as well. After 3 cycles, chemo was ceased due to worsening liver lesions. Anatomic and functional imaging were updated. Despite most of her metastatic disease being highly octreotide avid, there was a large liver lesion demonstrating high FDG uptake (the one biopsied above consistent with NEC). Again, the concern of disease de-differentiation within the liver was entertained, due to this large aggressive lesion non-responsive to

therapy. This lesion was highly FDG avid and less DOTATATE avid, while the remainder of the metastatic lesions were highly DOTATATE avid and FDG negative. She was referred again for liver directed therapies to address the most aggressive FDG avid lesion. She underwent another TARE procedure with Y-90 targeting the largest liver lesion in the left lobe, segments II/III. Following the procedure, she remained clinically well, asymptomatic with an ECOG of 0.

Her most recent CT scan of chest/abdomen and pelvis revealed stable hepatic metastasis in segment II/III with no adverse changes. Repeat FDG-PET scan performed at the same time, revealed interval decrease in metabolic activity of the dominant left liver lobe lesion, consistent with partial response to treatment, but interval increase in size and intensity of the right hepatic liver metastasis (Figure 4). Despite the mixed metabolic response in liver, seen on FDG PET, she remained clinically stable with preserved liver function and no metabolic derangement of liver parameters. She is currently awaiting PRRT with Lu177-Dotatate to address the remainder of her somatostatin avid metastatic disease. She remains on SSA agents.

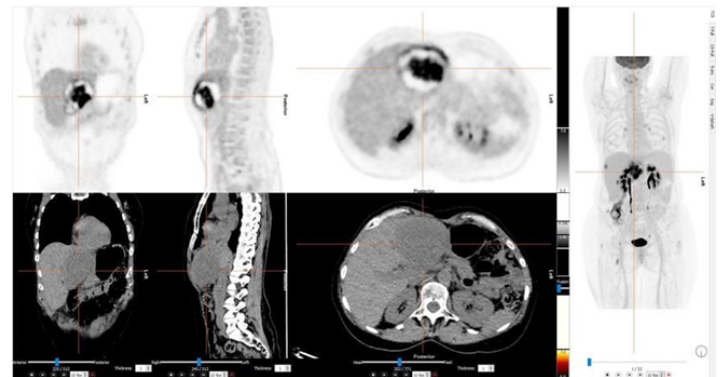


Figure 4: PET Body scan demonstrating positive response to therapy in the left liver lobe lesion, but increasing right liver lobe lesion.

Discussion

There is currently no guidance in literature, regarding management of recurrent metastatic NET in a transplanted liver patient. Furthermore, there are no case-report studies on outcomes of liver-directed therapies in transplanted liver patients with recurrent liver metastasis. This case is unique in several fronts, starting with the unusual pathology of an intrahepatic biliary GEP-NET. There are only few case reports of primary intra-biliary origin NETs and treatment algorithms differ by the centre. Definitive diagnosis is usually difficult to establish preoperatively [12]. In most case reports, complete surgical excision offers an optimal treatment

choice with no evidence for chemotherapy or radiotherapy's role in the management, by most centres. With respect to orthotopic liver transplant, most of the cases we identified in the literature that received liver transplant, were cases of secondary metastatic liver lesions due to another primary or recurrent metastatic HCC. Based on our literature search, we couldn't reference any other reported cases of localized intrahepatic biliary well-differentiated GEP-NETs, treated with liver transplant, that recurred in the transplanted liver. Additionally, our treatment strategy was individualized to this particular patient and involved a multidisciplinary approach, encompassing surgery, SSA agents, chemotherapy, liver directed procedures and radioligand based therapy.

Conclusion

Although an intrahepatic biliary GEP NETs are very rare and difficult to treat due to lack of specific guidelines, an early multimodality treatment approach guided by Tumor Board Decisions, could provide good long-term outcomes. This case proves that individualizing treatment strategies to patients' unique needs, can provide good durable long-term results, improving both PFS and quality of life.

A combination of SSA agents, TMZ based chemo and liver directed therapies, can provide good disease control, when offered both before and after surgery (complete hepatectomy and orthotopic liver transplant). Our patient did well on SSA, chemotherapy and localized liver treatments for nearly six years, before requiring liver removal and transplant. Despite disease recurrence and new evidence of distant metastatic disease, two years following liver transplant, she continued to do well on palliative therapies with SSA, TMZ based chemo re-challenge and more liver directed therapies. She continues to have an indolent disease course even four years post-transplant, despite widespread metastatic disease. It was not until four years post liver transplant, that she required systemic radionucleotide therapy with Lu-177 Dotatate. Furthermore, both localized application of Y-90 in selected liver lesions and systemic infusion of Lu-177-Dotatate, seems to be relatively safe in transplanted liver patients.

This case proves that an intrahepatic biliary neuroendocrine tumor, could have a very favourable clinical course on treatment. However due to rarity of biliary NETs in general, there is not enough data to guide patient's prognosis, and this is difficult to comment on [13]. Multi-modality approach systemic therapy offered both pre and post liver transplant, is a decent treatment strategy, as demonstrated in our patient. Despite lack of specific guidelines, this strategy deserves more attention, while being validated in future similar cases. It is important to consider all available tools in the treatment toolbox for GEP NETs and sequence them appropriately, guided by multidisciplinary Tumor Board discussions.

Conflict of Interest: Authors have no conflict of interest to disclose.

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