Case study

A Glimpse into Lutetium 177 therapy in Malignant insulinoma: Case report and review of literature
Abbreviated title: Malignant Insulinoma and Lutetium 177 therapy

Abstract

Background

Insulinomas are rare pancreatic neuroendocrine tumors, often benign, primarily causing hypoglycemia due to excess insulin secretion. This case report highlights the significance of early diagnosis and the effectiveness of a multimodal therapeutic approach in managing a metastatic malignant insulinoma, emphasizing the potential of somatostatin analogs, chemotherapy, and peptide receptor radionuclide therapy (PRRT) for improved outcomes.

Case Presentation

A 37-year-old, previously healthy woman has presented with recurrent hypoglycemia and severe neurological symptoms. Initially misdiagnosed and treated with prednisolone, she was eventually admitted to the intensive care unit due to hypoglycemia and hypoxia. A computed tomography (CT) scan revealed a 5.7 cm pancreatic tumor with multifocal liver and spleen metastases. A liver biopsy confirmed a well-differentiated neuroendocrine tumor (NET) grade 2. Treatment commenced with continuous glucose infusion, lanreotide, and short-acting octreotide injections, followed by palliative chemotherapy (capecitabine and temozolomide). The patient experienced significant clinical improvement, and subsequent follow-up showed partial resolution of liver lesions. Further management included PRRT with Lutetium-177-DOTATATE, which remarkably reduced tumor size and symptoms. The patient maintained euglycemia and clinical stability, with a progression-free survival exceeding 30 months.

Conclusions

This case underscores the successful management of a challenging metastatic malignant insulinoma using a combination of somatostatin analogs, chemotherapy, and PRRT. The sustained clinical improvement and progression-free survival demonstrate the potential of this multimodal approach in controlling the disease and enhancing the patient's quality of life. Further research and guidelines are needed to advance the management of metastatic insulinomas. This report emphasizes the importance of considering diverse treatment modalities to provide effective and personalized care for rare and complex endocrine tumors like malignant insulinoma.

Keywords:

Insulinoma, NET, malignant, metastatic, PRRT, Lutetium 177, capecitabine, lanreotide.

Introduction

Insulinomas are considered the most common functioning endocrine tumors of the pancreas. The rule of 10 implies that 10% of insulinomas are multiple, 5-10% are associated with the multiple endocrine neoplasia(MEN)-1 syndrome, and less than 10% can be malignant or otherwise metastatic (1).

Patients with insulinoma present with symptoms of hypoglycemia because of the elevated secretion of endogenous insulin, leading to neuroglycopenia and a surge of catecholamines. Neuroglycopenic symptoms can manifest as various neurological complaints, such as anxiety, dizziness, confusion, blurred vision, seizures, and coma.

Besides that, other signs and symptoms, including palpitations, diaphoresis, and tachycardia, which are caused by the release of catecholamines in response to low serum glucose levels, may be present (2).

One should suspect a diagnosis of insulinoma when applying Whipple's triad, which constitutes the presence of neuroglycopenia symptoms, documented hypoglycemia (plasma glucose < 50mg/dl), and alleviated symptomology upon glucose administration (3). Once confirmed, biochemical investigations are used to identify the plasma glucose, insulin, C-peptide, and proinsulin levels during a 72-h fast to assert the presence of endogenous cause hyperinsulinism (4).

After carrying out the biochemical confirmation of hyperinsulinism, different imaging modalities will be used to localize the tumor, including transabdominal ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). CT and MRI are reported to possess higher sensitivity (33%-64% and 40%-90%), respectively. MRI is generally superior to CT, especially when it is a requirement to detect extrapancreatic lesions (5).

During recent years, 68Ga tetraazacyclododecanetetraacetic acid-DPhe1-Tyr3-octreotate (DOTATATE)Positron emission tomography/computerized tomography (PET/CT), a functional imaging modality, has been employed to assess well-differentiated neuroendocrine tumors (NETs). It has become the preferred way for initial diagnosis, selecting patients for peptide receptor radionuclide therapy, assessing tumor heterogeneity, and localization of unknown primary tumors (6).

In terms of preoperative localization of resectable insulinomas, invasive testing methods like endoscopic ultrasound (EUS) and arterial stimulation and venous sampling (ASVS) have been found to be more effective than other approaches (7). Certain factors, such as tumor size (≥2 cm), tumor grading and staging (Ki-67 labeling>2%), p53 immunostaining, cytokeratin (CK) 19 status, and several molecular

features (including chromosomal instability; chromosomal loss of 3p or 6q; and chromosomal gain on 12q, 14q or 17pq), as well as the presence of involved lymph nodes or liver metastases, can be indicative of malignant disease and poor prognosis (7, 8).

Case description

Our case began as a previously healthy 37-year-old woman presented to King Hussein Cancer Center (KHCC) with a three-month history of recurrent hypoglycemia. She had experienced symptoms such as confusion, altered mental status, agitation, and aggressive behavior, which led to hospitalization on multiple occasions. No episodes of flushing, excessive sweating, or significant complaints of diarrhea were reported. The patient had initially been evaluated at hospitals in her native country, but due to limited resources, she had been misdiagnosed and treated with prednisolone for three months.

Upon arrival, the patient appeared agitated and confused, exhibiting a cushingoid appearance. Due to hypoxia and severe hypoglycemia, admitting the patient to the intensive care unit (ICU) was necessary. A continuous glucose infusion was started, even though the patient was not diagnosed with diabetes mellitus and was not taking any hypoglycemic medications, necessitating undergoing further assessment and evaluation. The endocrinology team evaluated the patient during the inpatient workup for hypoglycemia and determined that insulinoma was the most likely cause. The patient was given a continuous infusion of dextrose 25% to control hypoglycemia.

Computed tomography of the chest, abdomen, and pelvis (CT CAP) was conducted to investigate the underlying cause of hypoglycemia and hypoxia. The CT CAP revealed a pancreatic tumor measuring approximately 5.7 cm in size and multifocal metastatic lesions in the liver and spleen. Additionally, bilateral nonocclusive pulmonary embolisms were noted (Figures 1 and 2). By pursuing a liver biopsy, a well-differentiated neuroendocrine tumor (NET) grade 2 was confirmed (Figure 3). Immunohistochemical analysis of the tumor cells depicted positive staining for synaptophysin (Figure 4), chromogranin (Figure 5), and CDX2 (Figure 6), indicating their neuroendocrine origin. The Ki-67 proliferation index, a marker of tumor cell proliferation, was found to be 3%, indicating a low rate of cell division in the tumor (Figure 7). Echocardiography results were ordinary, showing no evidence of valvular dysfunction.

Upon the decision of the gastrointestinal **multi-disciplinary conference (MDC)** and hepatobiliary surgical specialist, lanreotide 120 mg and short-acting octreotide injections were initiated since a debulking surgery was not an option due to the extensive metastatic disease. In addition, palliative chemotherapy with capecitabine and temozolomide was administered. After the first cycle, the patient's

mental status and blood glucose reading started normalizing, and no more hypoglycemic attacks were experienced, illustrating the evident significant clinical improvement.
A follow-up CT CAP after the second cycle revealed partial resolution of the metastatic lesions in the right upper lobe, smaller splenic lesions, and stable size of the pancreatic tail mass, but progression of some liver lesions. However, chemotherapy administration proceeded as planned as the patient was clinically improving. The course of chemotherapy was uneventful, with mild chemotherapy-related toxicity that the patient tolerated well.

After receiving six cycles of capecitabine and temozolomide, follow-up CT and PET/CT DOTATOC scans showed an increase in the size of some liver lesions. However, the patient was clinically stable with normal blood sugar levels (Figure 8). It was then decided to initiate peptide receptor radionuclide therapy (PRRT)-Lutetium-177 along with monthly Lanreotide. The patient was deemed fit for radioactive lutetium and received four cycles of Lutetium-177-DOTATATE, administered at 10-week intervals. The patient still receives a sustained dose of 120 mg of lanreotide, even after completing the four cycles of Lutetium-177-DOTATATE. Administering lanreotide in the dose mentioned above remains in the plan as long as she is clinically stable.

A follow-up PET/CT DOTATOC at three months after the last cycle of Lutetium-177-DOTATATE showed a decrease in the size and number of liver lesions, significant regression in the size of the pancreatic tail mass lesion, and distal part of the pancreatic body, significant regression in the size of splenic lesions, and almost complete resolution of the left retrocrural and paraaortic lymph nodes(Figure 9).
As previously mentioned, the patient has been undergoing regular PET/CT follow-ups at 3-month intervals while maintaining a monthly dose of 120 mg of lanreotide. As of this report, the latest follow-up visit occurred in December 2022, marking approximately two years of follow-up since her last PRRT session. The patient has remained euglycemic and symptom-free, and her last PET/CT follow-up still showed an excellent response to treatment, indicating a well-controlled disease. The somatostatin receptor-positive malignant pancreatic tail mass and numerous metastatic hepatic and splenic lesions left external iliac and retrocrural lymph nodes demonstrated interval regressive features compared to the prior scan, with no new lesions detected. In addition, her progression-free survival (PFS) is over 30 months.

Discussion

Surgical resection is the primary treatment for insulinomas, typically performed after a confirmed diagnosis. Enucleation is typically performed for small, benign, and singular insulinomas more than 2-3 mm from the central pancreatic duct and significant vessels. In cases where tumors are large, highly suspicious of malignancy, or have metastasized, pancreatectomy and lymph node resection may be necessary (8).

A retrospective study by Fine et al. investigated the CAPTEM (capecitabine and temozolomide) administration for metastatic well-differentiated neuroendocrine tumors. It has become apparent that CAPTEM is highly effective, generally accepted, and well tolerated by patients. Cytotoxicity from capecitabine arises from reducing the thymidine pools through inhibiting thymidylate synthetase via -FdUMP. Temozolomide, however, is a methylating agent, which methylates the N7 guanine position, and to a lesser extent, the O6 guanine position, adds synergistically to the efficacy of the treatment (9). Arrivi et al. confirmed that patients with pancreatic neuroendocrine tumors (PNETs) responded favorably to the CAPTEM regimen (10). Myelosuppression in the form of neutropenia and gastrointestinal upset such as nausea, diarrhea, and vomiting are attributed toxicities of the regimen (10, 11).

Somatostatin, an amino acid inhibitor of various hormones, and somatostatin analogs (SSAs) exert their effect by binding into somatostatin receptors (SSTRs), which are expressed by most neuroendocrine tumors (NETs) (12). Octreotide, a short-acting SSA, and lanreotide, a long-acting SSA (13-15), potentiate efficacy in managing hypoglycemia in an unpredictable manner (16-21). However, they may paradoxically worsen hypoglycemia temporarily by inhibiting glucagon secretion. SSAs have been linked to disease stabilization, significant tumor shrinkage, and prolonged progression-free survival (PFS) (22-24). Somatostatin and its analogs have demonstrated antiproliferative potential in vitro and experimental tumor models, leading to various studies in patients with metastatic endocrine tumors that are typically unresponsive to conventional chemotherapy. The most favorable outcome was tumor growth stabilization lasting from several months to a few years, observed in 30-70% of patients (25). Although well-tolerated gastrointestinal complaints such as nausea, bloating, abdominal discomfort, loose stools, and fat malabsorption may occur when SSAs are initiated, these symptoms tend to improve over time (26, 27).

Peptide receptor radionuclide therapy (PRRT) is a form of systemic radiotherapy that targets tumor cells expressing high levels of SSTRs (28). The antiproliferative effect of PRRT requires specific binding to somatostatin receptors (SSTRs), specifically subtypes sst2a and sst5, via a radiolabeled somatostatin analog. This results in tumor cell death, rapid elimination of residual radioactivity, and extended retention of radioactivity in the tumor cells. It is important to note that the expression of SSTR subtypes in the tumor cells, which determines the binding of the radioligand, is a critical prerequisite for the success of PRRT (29).

One example of PRRT used in treating this patient's disease is 177 Lutetium-DOTATATE, Lu 177 Dotatate is a Peptide receptor radionuclide agent; a lutetium 177 radiolabeled tetraazacyclododecane-tetra-acetic acid (DOTA)-somatostatin analog conjugate consisting of the somatostatin analog octreotide linked to a chelator (DOTA) (30-34). It mainly treats somatostatin receptor-positive neuroendocrine tumors of gastroenteropancreatic origin (GEP-NET), including foregut, midgut, and hindgut neuroendocrine tumors (30, 31). It has been demonstrated to be significantly efficacious in treating advanced, low-to-intermediate-grade GEP-NETs (35). The therapeutic effect of 177Lu-DOTATATE is essential in controlling tumor growth in non-functional small intestine NET that progressively spreads and in providing symptom control and regression.

This effect occurs months before the tumor begins to respond (28).The presence of abundant somatostatin receptor type 2 (SST2) expression is a crucial factor in predicting the success of PRRT with 177-Lu-DOTATATE for neuroendocrine neoplasms (NEN). Additionally, the tumoral grade is another prognostic factor that affects the outcome of PRRT. Low-grade NENs (G1, G2, and low G3) with adequate somatostatin receptor (SST) expression tend to have a higher affinity to 177-Lu-DOTATATE. In an ideal candidate for 177Lu-DOTATATE treatment, the following conditions should be met: the presence of metastatic inoperable and incurable NETs, absence of obstruction in the surrounding structures, high 68Ga-DOTATATE PET uptake (=< liver), relatively limited hepatic tumor burden, and a Ki67 index of less than 20% (36). Since it came to light that bone marrow is the organ responsible for adjusting the dose in this mode of therapy, in patients with high-burden metastatic disease to the bone marrow, dose reduction should be considered (37, 38). Adverse events associated with PRRT and 177Lu-DOTATATE are -but not limited to hematological toxicities, myelodysplastic syndrome, and kidney and liver failure (29, 39).

Several studies have investigated the effectiveness of lutetium-177 in treating malignant insulinoma, with promising results. One of these studies is a case report that presents the cases of two men diagnosed with inoperable malignant insulinoma and hepatic metastases and shows that the Use of

Lutetium-177 octreotate, and in one case everolimus, successfully achieved normoglycemia, facilitating safe discharge from hospital. Both men also had a regression in the size and number of hepatic metastases (40). Another study shed light on the response of 177Lu-Dotatate in treating functioning neuroendocrine tumors. It concluded that treatment with 177Lu-DOTATATE is a safe and effective therapy resulting in radiological, symptomatic, and biochemical responses in a high percentage of patients with metastatic functioning PNETs. Hormonal crises occur relatively frequently, and preventive therapy should be considered before and/or during PRRT (41).

Kumar et al. reported a case of a 96-year-old man diagnosed with insulin-dependent type 2 diabetes mellitus who experienced recurrent hypoglycemia despite discontinuing insulin treatment. The patient was found to have metastatic insulinoma, which resulted in confirmed inappropriate endogenous hyperinsulinemia. After carefully evaluating treatment options, management with four cycles of Lutate (177-Lutetium-DOTA0-Tyr3-octreotate) was commenced, leading to the resolution of hypoglycemia and ongoing clinical, biochemical, and radiological response six years after (42).

Magalhaes et al. in Italy described the cases of four patients with inoperable malignant insulinomas and poorly controllable hypoglycemia, where all patients were treated with 177Lu-DOTA-TATE after conventional therapies failed to control disease progression and symptoms. The first patient reception of PRRT culminated in a clinical improvement in tumor load reduction after the second, lasting for 13 months. Notably, after the second patient was administered 177Lu-DOTA-TATE, her hypoglycemic symptoms' severity and frequency devolved throughout 15 months of therapy. 6.5 years after being diagnosed with malignant insulinoma with hepatic dissemination, the third patient began receiving 177Lu-DOTATATE PRRNT, after which she became asymptomatic and demonstrated radiologically improving disease. The fourth patient witnessed a clinical resolution of her symptoms three days after the first cycle of 177Lu-DOTATATE PRRNT, and after the second cycle, evident imaging improvement was reported. Sixteen months after utilizing PRRNT, she exhibits euglycemia, and her disease is in remission. (43).

Conclusion

The author's case details the successful management of a previously healthy 37-year-old female with metastatic malignant insulinoma. Treatment involved a combination of lanreotide 120 mg and six cycles

of chemotherapy constituent of capecitabine and temozolomide, and four cycles of Lutetium-177-DOTATATE, highlighting that the patient is still actively receiving a monthly dose of 120 mg of lanreotide after finishing the four cycles of Lutetium-177-DOTATATE. The efficacy of this treatment manifests as the patient retains a progression-free survival (PFS) of more than 30 months, in addition to remarkably sustained clinical and radiological improvement, along with the absence of hypoglycemia confirmed during her last follow-up visit in December 2022.

However, even with the graveness of a metastatic insulinoma in terms of size, spread, and symptomology, medical regimens such as SSA, chemotherapy, i.e., CAPTEM, and PRRT, i.e., 177Lu-DOTATATE, have proven effective in controlling the disease and providing progression-free intervals, where the symptoms are no longer a setback, in addition to enhancing the quality-of-life (QoL). Nevertheless, due to the rarity of malignant insulinoma and the novelty of PRRT and somatostatinanalogs, it is recommended that further studies be carried out to provide crystal-clear guidelines for managing metastatic–malignant- insulinoma.

Abbreviations

-Peptide receptor radionuclide therapy (PRRT)

-Computed tomography (CT)

-Neuroendocrine tumor (NET)

-Multiple endocrine neoplasia (MEN)

-Magnetic resonance imaging (MRI)

-Positron emission tomography/computerized tomography (PET/CT)

-Endoscopic ultrasound (EUS)

-Arterial stimulation and venous sampling (ASVS)

-Cytokeratin (CK)

-King Hussein Cancer Center (KHCC)

-Intensive care unit (ICU)

-Computed tomography of the chest, abdomen, and pelvis (CT CAP)

-Multi-disciplinary conference (MDC)

-Progression-free survival (PFS)

-Capecitabine and temozolomide (CAPTEM)

-Pancreatic neuroendocrine tumors (PNETs)

-Somatostatin analogs (SSAs)

-Somatostatin receptors (SSTRs)

-Gastroenteropancreaticneuroendocrine tumor (GEP-NET)

-Neuroendocrine neoplasms (NEN)

-Peptide receptor radionuclide therapy (PRRNT)

-Quality-of-life (QoL)

-Standard uptake value (SUV)

Declaration

-Ethical Approval and Consent to Participate:

Ethical approval for this study was obtained from the institutional review board of King Hussein Cancer Center (KHCC). This case report was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information was performed in a Health Insurance Portability and Accountability Act (HIPAA)-compliant manner. Written consent to participate was obtained from the participant.

Consent for publication:

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

-Availability of supporting data

Not applicable.

-Additional information

All data underlying the results is available as part of the article and no additional source data is required.

-Data Availability:

The data for this project is confidential but may be obtained with Data Use Agreements with King Hussein Cancer Center (KHCC).

-Code of availability:

Not applicable

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Figure (1):

The image shows a large splenic lesion measuring about 3.7 x 3.6 cm in maximum axial dimensions with SUV max 64.3, in addition to a large soft tissue mass lesion within the tail of the pancreas measuring about 4.8 x 2.5 cm in maximum axial dimensions,exhibiting abnormal DOTATOC uptake with SUV max 83.

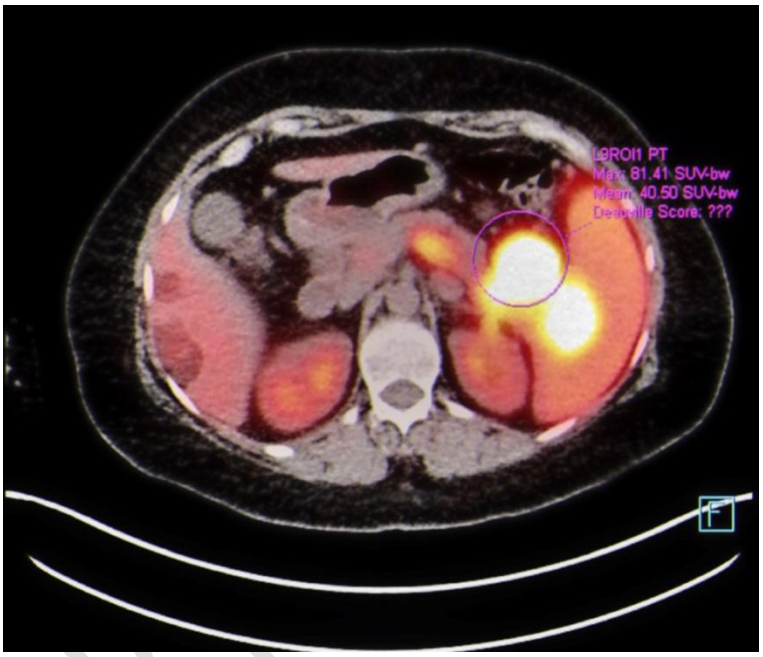


Figure (2):

The image is another cut at presentation, showing innumerable hypodense liver lesions scattered within both liver lobes, all with intense Ga68-DOTATOC uptake, with up to 60.4 SUV max.

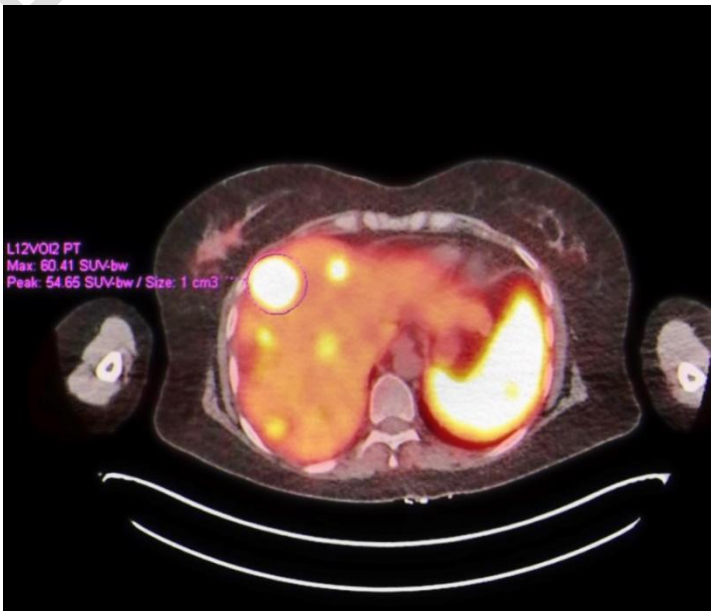


Figure (3):

The figure confirms the existence of a well-differentiated neuroendocrine tumor (NET) grade using H&E stain.

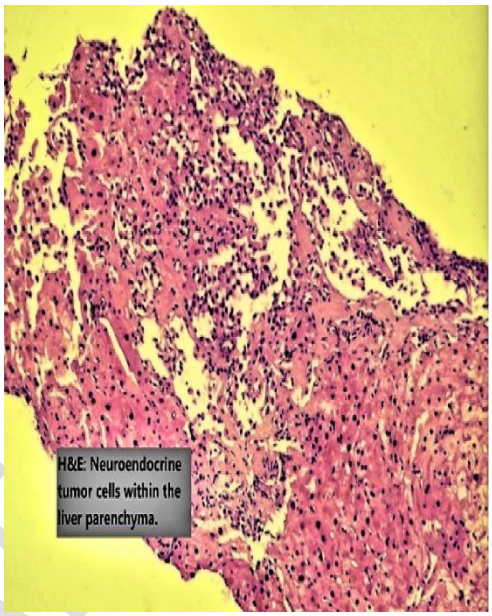


Figure (4):

The figure portrays the tumor cells exhibiting positive staining when subjected to the immunohistochemical stain of synaptophysin.

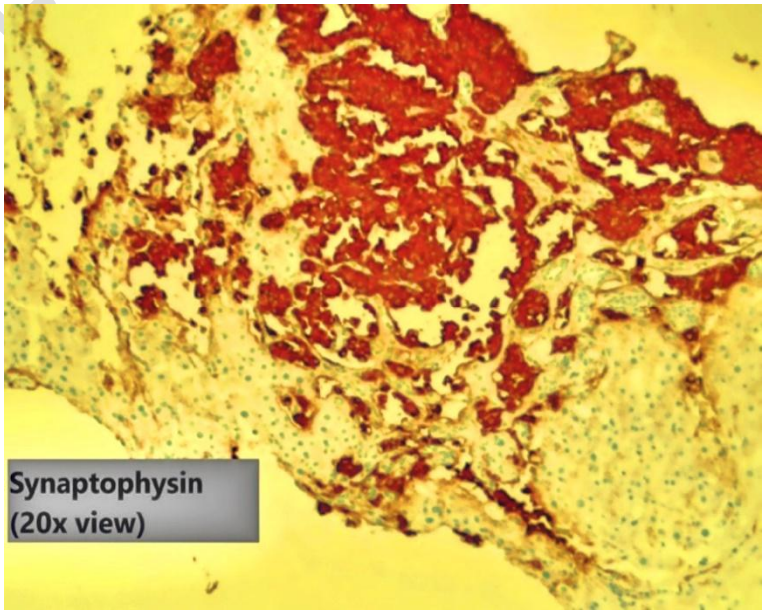


Figure (5):

The figure shows the tumor cells positively stained with chromogranin.

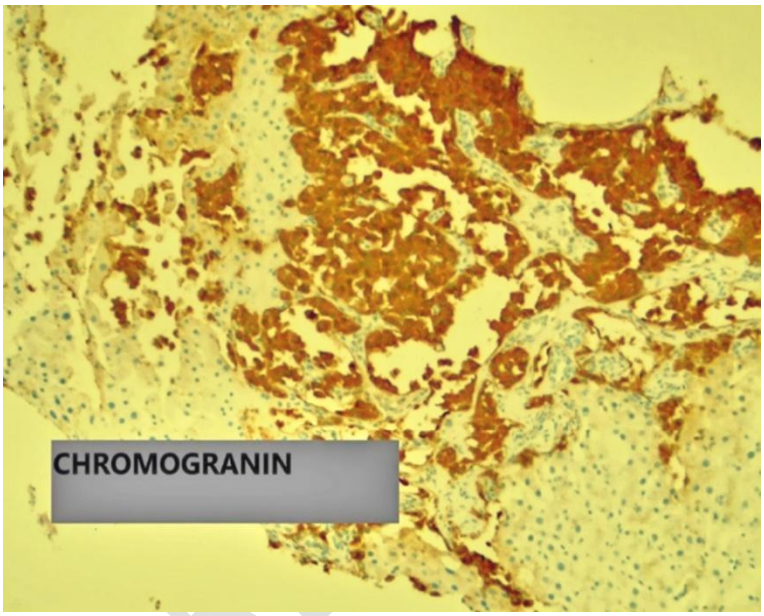


Figure (6):

The tumors cells presented within this figure exhibit CDX2 stain.

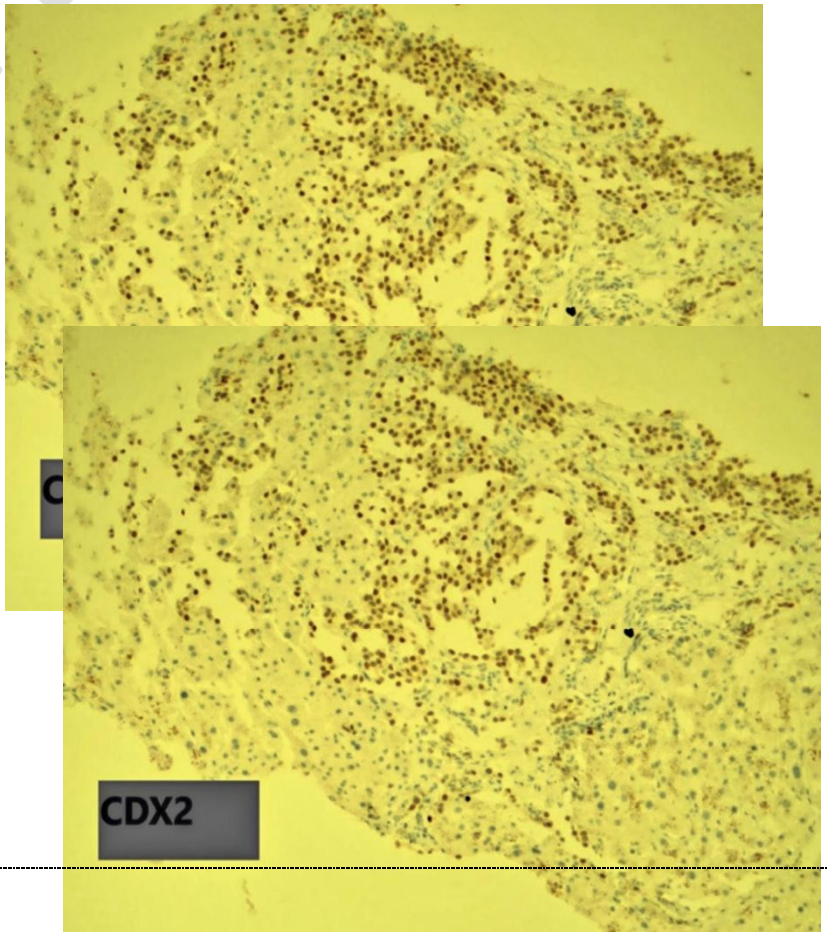


Figure (7):

This illustration displays the tumors cell depicting the Ki-67 proliferation index.

Figure (8):

The image represents a follow-up Pet scan after 6 cycles of chemotherapy showing a less prominent appearance of the previously mentioned large splenic lesion, currently measuring about 2.1 cm on fused images with SUV max=44.43 compared to 3.63 x 3.5 cm & SUV max 80 previously. Moreover, it emphasizes a less prominent appearance of the previously mentioned large soft tissue mass lesion within the tail of pancreas, currently is measuring about 3.7x2.7cm in maximum axial dimensions with SUV max=44.3 compared to 4.67x2.7 cm & SUV max 81 previously.

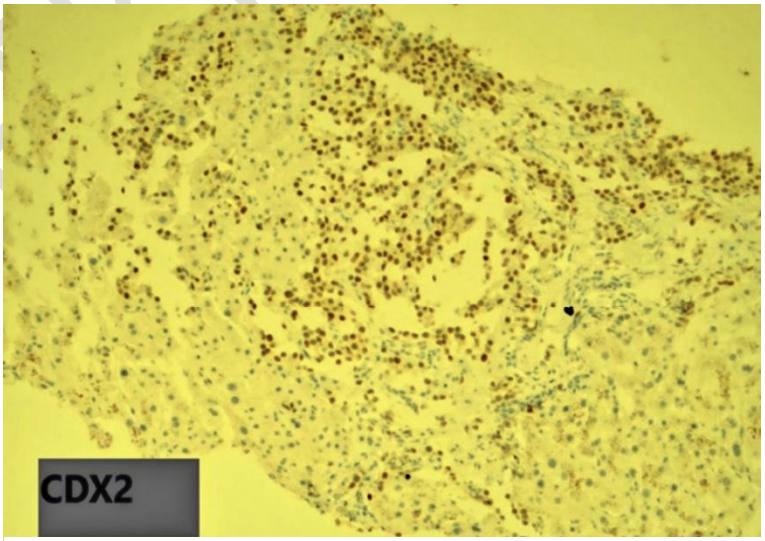
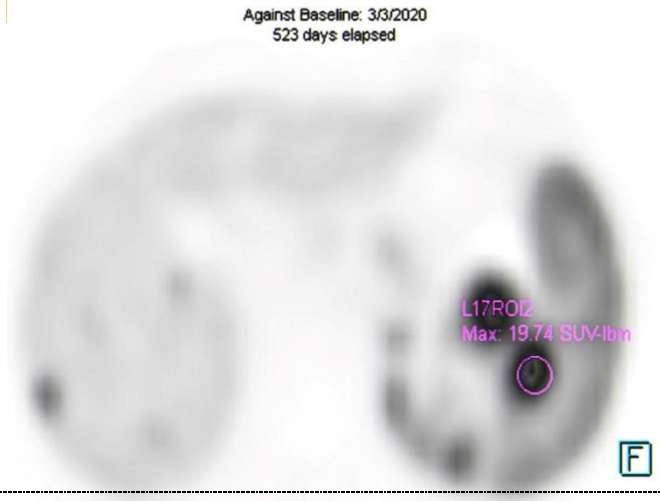


Figure (9):



This is a follow-up Pet scan after 4 doses Lu177 DOTATOC showcasing decrease in the size and number of liver lesions, significant regression in the size of the pancreatic tail mass lesion, distal part of the pancreatic body and splenic lesions. Furthermore, it highlights an almost complete resolution of the left retrocrural and paraaortic lymph nodes.