

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

Abstract

Background:

Insulinomas are a rare type of pancreatic neuroendocrine tumors, characterized by their frequent benign nature and propensity to induce hypoglycemia through excessive insulin secretion. This case report underscores the importance of timely diagnosis and the advantages of a multifaceted therapeutic strategy for treating metastatic malignant insulinomas. This report highlights the promise of somatostatin analogs, chemotherapy, and peptide receptor radionuclide therapy (PRRT) in achieving better patient outcomes.

Case Presentation:

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

Conclusions:

This case highlights the successful management of metastatic malignant insulinoma using a combination of somatostatin analogs, chemotherapy, and PRRT. Sustained clinical improvement and progression-free survival demonstrated the potential of this multimodal approach in controlling the disease and enhancing the patient's quality of life. Further research and guidelines are required to improve the

management of metastatic insulinoma. This report emphasizes the importance of considering diverse treatment modalities to provide effective and personalized care for rare and complex endocrine tumors such as malignant insulinoma.

Keywords:

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

Introduction

Insulinomas are the most common endocrine tumors of the pancreas. A rule of 10 implies that 10% of insulinomas are multiple, 5-10% are associated with 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 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.

In addition, 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).

A diagnosis of insulinoma should be suspected when applying Whipple's triad, which constitutes the presence of neuroglycopenia symptoms, documented hypoglycemia (plasma glucose < 50 mg/dl), and alleviated symptoms 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 hyperinsulinism (4).

After 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 have been reported to possess higher sensitivity (33%-64% and 40%-90%), respectively. MRI is superior to CT, particularly when detecting extrapancreatic lesions (5).

In recent years, 68Ga tetraazacyclododecanetetraacetic acid-DPhe1-Tyr3-octreotate (DOTATATE) positron emission tomography/computed tomography (PET/CT), a functional imaging modality, has been employed to assess well-differentiated neuroendocrine tumors

(NETs). It has become the preferred method for initial diagnosis, selecting patients for peptide receptor radionuclide therapy, assessing tumor heterogeneity, and localizing unknown primary tumors (6).

In terms of preoperative localization of resectable insulinomas, invasive testing methods such as 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 with a previously healthy 37-year-old woman who presented to the King Hussein Cancer Center (KHCC) with a three-month history of recurrent hypoglycemia. She 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 was misdiagnosed and treated with prednisolone for three months.

Upon arrival, the patient appeared agitated and confused with a cushingoid appearance. Due to hypoxia and severe hypoglycemia, admission of the patient to the intensive care unit (ICU) was necessary. Continuous glucose infusion was started even though the patient was not diagnosed with diabetes mellitus and was not taking any hypoglycemic medications, necessitating 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 administered a continuous infusion of dextrose 25% to control hypoglycemia. Computed tomography of the chest, abdomen, and pelvis (CT CAP) was performed to investigate the underlying cause of hypoglycemia and hypoxia. Computed tomography (CT) revealed a pancreatic tumor measuring approximately 5.7 cm in size and multifocal metastatic

lesions in the liver and spleen. Additionally, bilateral non-occlusive pulmonary embolisms were noted (Figures 1 and 2). Liver biopsy confirmed a well-differentiated neuroendocrine tumor (NET) grade 2 (Figure 3). Immunohistochemical analysis of the tumor cells showed positive staining for synaptophysin (Figure 4), chromogranin (Figure 5), and CDX2 (Figure 6), indicating neuroendocrine origin. The Ki-67 proliferation index, a marker of tumor cell proliferation, was 3%, indicating a low rate of cell division in the tumor (Figure 7). Echocardiographic results were normal, 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 as debulking surgery was not an option due to the extensive metastatic disease. Palliative chemotherapy with capecitabine and temozolomide was administered. After the first cycle, the patient's mental status and blood glucose readings started normalizing, and no more hypoglycemic attacks were experienced, illustrating 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 a stable size of the pancreatic tail mass, but progression of some liver lesions. However, chemotherapy was administered as planned, as the patient was clinically improving. The course of chemotherapy was uneventful, with mild chemotherapy-related toxicity that the patient tolerated.

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 and had normal blood sugar levels (Figure 8). It was then decided to initiate peptide receptor radionuclide therapy (PRRT) with 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 received a sustained dose of 120 mg lanreotide, even after completing four cycles of Lutetium-177-DOTATATE. Administering lanreotide at the dose mentioned above remains in the plan if the patient 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 para-aortic lymph nodes (Figure 9).

As previously mentioned, the patient underwent regular PET/CT follow-ups at 3-month intervals while maintaining a monthly dose of 120 mg lanreotide. As of this report, the latest follow-up visit occurred in December 2022, marking approximately two years of follow-up since the last PRRT session. The patient remained euglycemic and symptom-free, and her last PET/CT follow-up 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 in the left external iliac and retrocrural lymph nodes demonstrated interval regressive features compared with the prior scan, with no new lesions detected. In addition, progression-free survival (PFS) was > 30 months.

Discussion

Surgical resection is the primary treatment for insulinomas, which is 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 the significant vessels. In cases where tumors are large, highly suspicious for malignancy, or have metastasized, pancreatectomy and lymph node resection may be necessary (8).

A retrospective study by Fine et al. investigated the administration of capecitabine and temozolomide (CAPTEM) for metastatic well-differentiated neuroendocrine tumors. It has become apparent that CAPTEM is highly effective, accepted, and well-tolerated by patients. Cytotoxicity from capecitabine arises from the reduction of thymidine pools through the inhibition of thymidylate synthetase via -FdUMP. However, temozolomide is a methylating agent that methylates the N7 guanine position, and to a lesser extent, the O6 guanine position, synergistically adds 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 to the toxicities of the regimen (10, 11).

Somatostatin, an amino acid inhibitor of various hormones, and somatostatin analogs (SSAs) exert their effects by binding to 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), can potentially be used to manage hypoglycemia in an unpredictable manner (16-21). However, they may paradoxically temporarily worsen hypoglycemia 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 in vitro and in experimental tumor models, leading to numerous 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 elevated 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 tumor cells. It is important to note that the expression of SSTR subtypes in tumor cells, which determines the binding of the radioligand, is a critical prerequisite for the success of PRRT (29).

An example of PRRT used to treat this patient's disease is ¹⁷⁷lutetium-DOTATATE. Lu 177 Dotatate is a Peptide receptor radionuclide agent; a lutetium 177 radiolabeled tetraazacyclododecane-tetraacetic 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 efficient in treating advanced low-to-intermediate-grade GEP-NETs (35). The therapeutic effect of ¹⁷⁷Lu-DOTATATE is essential for controlling tumor growth

in non-functional small intestine NET that progressively spreads and for providing symptom control and regression.

This effect occurs months before the tumor begins to respond (28). 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). Tumor 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 tended to have a higher affinity for ¹⁷⁷-Lu-DOTATATE. In an ideal candidate for ¹⁷⁷Lu-DOTATATE treatment, the following conditions should be met: presence of metastatic inoperable and incurable NETs, absence of obstruction in the surrounding structures, high ⁶⁸Ga-DOTATATE PET uptake (\leq liver), relatively limited hepatic tumor burden, and a Ki67 index of less than 20% (36). Since it became known 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 the treatment of 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 showed that the Use of Lutetium-177 octreotate and in one case everolimus successfully achieved normoglycemia, facilitating safe discharge from the hospital. Both men also showed regression in the size and number of hepatic metastases (40). Another study shed light on the response of ¹⁷⁷Lu-Dotatate in the treatment of functioning neuroendocrine tumors. It was concluded that 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 the 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 confirmed

inappropriate endogenous hyperinsulinemia. After careful evaluation of 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 later (42).

Magalhaes et al. described the cases of four patients with inoperable malignant insulinomas and poorly controllable hypoglycemia, all of whom were treated with 177Lu-DOTA-TATE after conventional therapies failed to control disease progression and symptoms. The first patient received PRRT, culminating 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 symptom severity and frequency resolved over 15 months of therapy. 6.5 years after the diagnosis of malignant insulinoma with hepatic dissemination, the third patient began receiving 177Lu-DOTATATE PRRNT, after which she became asymptomatic and demonstrated radiological improvement. The fourth patient experienced clinical resolution of her symptoms three days after the first cycle of 177Lu-DOTATATE PRRNT, and after the second cycle, imaging improvement was evident. Sixteen months after PRRNT, she exhibited euglycemia, and her disease was in remission. (43).

Conclusion

The management of a 37-year-old female patient with metastatic malignant insulinoma was successfully carried out through a combination of lanreotide 120 mg and six cycles of chemotherapy consisting of capecitabine and temozolomide, as well as four cycles of Lutetium-177-DOTATATE. The patient is currently receiving a monthly dose of 120 mg lanreotide and has completed four cycles of Lutetium-177-DOTATATE. The efficacy of this treatment is evidenced by the patient's progression-free survival (PFS) of over 30 months, a sustained clinical and radiological improvement, and the absence of hypoglycemia confirmed during her last follow-up visit in December 2022. Although metastatic insulinomas are serious because of their size, spread, and symptomology, medical regimens such as SSA, chemotherapy (iCAPTEM), and PRRT (177Lu-DOTATATE) have proven effective in controlling the disease, providing progression-free intervals, and improving the quality of life (QoL) of the patient. However, further studies are

recommended to provide clear guidelines for managing metastatic malignant insulinoma because of the rarity of this condition and the novelty of PRRT and somatostatin analogs.

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)
- Gastroenteropancreatic neuroendocrine tumor (GEP-NET)
- Neuroendocrine neoplasms (NEN)
- Peptide receptor radionuclide therapy (PRRT)
- Quality-of-life (QoL)
- Standard uptake value (SUV)

Declaration

-Acknowledgements

Not Applicable.

-Disclosure statement

The authors reported no potential conflict of interest.

-Ethical Approval

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.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images

-Availability of supporting data

Not applicable.

-Competing interests

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.

-Authors' contributions

KA: supervised and provided the primary draft

RA and YA: contributed equally to editing and writing the manuscript.

HM, ZO, MH, and MA: contributed equally to the images and figures within the manuscript.

References

1. Marek, B., Kajdaniuk, D., Kos-Kudła, B., Foltyn, W., Borgiel-Marek, H., Matyja, V., & Pakuła, D. (2007). Insulinoma--diagnostyka i leczenie [Insulinoma--diagnosis and treatment]. *Endokrynologia Polska*, 58(1), 58–62.
2. Mittendorf, E. A., Liu, Y. C., & McHenry, C. R. (2005). Giant insulinoma: case report and review of literature. *The Journal of clinical endocrinology and metabolism*, 90(1), 575–580. <https://doi.org/10.1210/jc.2004-0825>
3. Shao, Y., Qu, Y. Q., Wang, X. L., Song, Z. G., Guo, Q. H., Dou, J. T., Ba, J. M., Lü, Z. H., & Mu, Y. M. (2016). Malignant insulinoma: Report of 6 patients and literature review. *Neuro endocrinology letters*, 37(3), 189–192.
4. de Herder, W. W., & Hofland, J. (2023). Insulinoma. In K. R. Feingold (Eds.) et. al., *Endotext*. MDText.com, Inc.
5. Okabayashi, T., Shima, Y., Sumiyoshi, T., Kozuki, A., Ito, S., Ogawa, Y., Kobayashi, M., & Hanazaki, K. (2013). Diagnosis and management of insulinoma. *World journal of gastroenterology*, 19(6), 829–837. <https://doi.org/10.3748/wjg.v19.i6.829>
6. Sanli, Y., Garg, I., Kandathil, A., Kendi, T., Zanetti, M. J. B., Kuyumcu, S., & Subramaniam, R. M. (2018). Neuroendocrine Tumor Diagnosis and Management: ⁶⁸Ga-DOTATATE PET/CT. *American Journal of Roentgenology*, 211(2), 267–277. <https://doi.org/10.2214/ajr.18.19881>
7. Lee, C., Lee, G., Kim, D., Kim, N., Kim, S. W., & Song, K. H. (2003). A Large Malignant Insulinoma: Case Report with Endosonographic, Immunohistochemical and Ultrastructural Features. *The Korean Journal of Internal Medicine*, 18(1), 45–49. <https://doi.org/10.3904/kjim.2003.18.1.45>
8. Giannis, D., Moris, D., Karachaliou, G. S., Tsilimigras, D. I., Karaolanis, G., Papalampros, A., & Felekouras, E. (2020). Insulinomas: from diagnosis to treatment. A review of the literature. *Journal of B.U.ON. : official journal of the Balkan Union of Oncology*, 25(3), 1302–1314.

9. De Herder, W. W., Van Schaik, E., Kwekkeboom, D. J., & Feelders, R. A. (2011). New therapeutic options for metastatic malignant insulinomas. *Clinical Endocrinology*, 75(3), 277–284. <https://doi.org/10.1111/j.1365-2265.2011.04145.x>
10. Arrivi, G., Verrico, M., Roberto, M., Barchiesi, G., Faggiano, A., Marchetti, P., Mazzuca, F., & Tomao, S. (2022). Capecitabine and Temozolomide (CAPTEM) in Advanced Neuroendocrine Neoplasms (NENs): A Systematic Review and Pooled Analysis. *Cancer management and research*, 14, 3507–3523. <https://doi.org/10.2147/CMAR.S372776>
11. Kunz, P. L., Graham, N. T., Catalano, P. J., Nimeiri, H. S., Fisher, G. A., Longacre, T. A., Suarez, C. J., Martin, B. A., Yao, J. C., Kulke, M. H., Hendifar, A. E., Shanks, J. C., Shah, M. H., Zalupski, M. M., Schmulbach, E. L., Reidy-Lagunes, D. L., Strosberg, J. R., O'Dwyer, P. J., & Benson, A. B., 3rd (2023). Randomized Study of Temozolomide or Temozolomide and Capecitabine in Patients with Advanced Pancreatic Neuroendocrine Tumors (ECOG-ACRIN E2211). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 41(7), 1359–1369. <https://doi.org/10.1200/JCO.22.01013>
12. Reubi, J. C., Kvols, L. K., Waser, B., Nagorney, D. M., Heitz, P. U., Charboneau, J. W., Reading, C. C., & Moertel, C. (1990). Detection of somatostatin receptors in surgical and percutaneous needle biopsy samples of carcinoids and islet cell carcinomas. *Cancer research*, 50(18), 5969–5977.
13. Eriksson, B., Renstrup, J., Imam, H., & Oberg, K. (1997). High-dose treatment with lanreotide of patients with advanced neuroendocrine gastrointestinal tumors: clinical and biological effects. *Annals of oncology : official journal of the European Society for Medical Oncology*, 8(10), 1041–1044. <https://doi.org/10.1023/a:1008205415035>
14. Tomassetti, P., Migliori, M., & Gullo, L. (1998). Slow release lanreotide treatment in endocrine gastrointestinal tumors. *The American journal of gastroenterology*, 93(9), 1468–1471. https://doi.org/10.1111/j.1572-0241.1998.465_q.x
15. Toumpanakis, C., & Caplin, M. E. (2013). Update on the role of somatostatin analogs for the treatment of patients with gastroenteropancreatic neuroendocrine tumors. *Seminars in oncology*, 40(1), 56–68. <https://doi.org/10.1053/j.seminoncol.2012.11.006>
16. Romeo, S., Milione, M., Gatti, A., Fallarino, M., Corleto, V., Morano, S., & Baroni, M. G. (2006). Complete clinical remission and disappearance of liver metastases after treatment with somatostatin analogue in a 40-year-old woman with a malignant insulinoma positive for somatostatin receptors type 2. *Hormone research*, 65(3), 120–125. <https://doi.org/10.1159/000091408>
17. Okamoto, M., Kishimoto, M., Takahashi, Y., Osame, K., Noto, H., Yamamoto-Honda, R., Kajio, H., Tokuhara, M., Edamoto, Y., Endo, H., Igari, T., Kubota, K., & Noda, M. (2013). A case of malignant insulinoma: successful control of glycemic fluctuation by replacing octreotide injections with octreotide LAR injections. *Endocrine journal*, 60(8), 951–957. <https://doi.org/10.1507/endocrj.ej13-0025>
18. Hirshberg, B., Cochran, C., Skarulis, M. C., Libutti, S. K., Alexander, H. R., Wood, B. J., Chang, R., Kleiner, D. E., & Gorden, P. (2005). Malignant insulinoma: spectrum of unusual clinical features. *Cancer*, 104(2), 264–272. <https://doi.org/10.1002/cncr.21179>

19. Healy, M. L., Dawson, S. J., Murray, R. M., Zalcborg, J., & Jefford, M. (2007). Severe hypoglycaemia after long-acting octreotide in a patient with an unrecognized malignant insulinoma. *Internal medicine journal*, 37(6), 406–409. <https://doi.org/10.1111/j.1445-5994.2007.01371.x>
20. Stehouwer, C. D., Lems, W. F., Fischer, H. R., Hackeng, W. H., & Naafs, M. A. (1989). Aggravation of hypoglycemia in insulinoma patients by the long-acting somatostatin analogue octreotide (Sandostatin). *Acta endocrinologica*, 121(1), 34–40. <https://doi.org/10.1530/acta.0.1210034>
21. Jawiarczyk, A., Bolanowski, M., Syrycka, J., Bednarek-Tupikowska, G., Kałużny, M., Kołodziejczyk, A., & Domosławski, P. (2012). Effective therapy of insulinoma by using long-acting somatostatin analogue. A case report and literature review. *Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association*, 120(2), 68–72. <https://doi.org/10.1055/s-0031-1287792>
22. Rinke, A., Müller, H. H., Schade-Brittinger, C., Klose, K. J., Barth, P., Wied, M., Mayer, C., Aminossadati, B., Pape, U. F., Bläker, M., Harder, J., Arnold, C., Gress, T., Arnold, R., & PROMID Study Group (2009). Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 27(28), 4656–4663. <https://doi.org/10.1200/JCO.2009.22.8510>
23. Caplin, M. E., Pavel, M., Ćwikła, J. B., Phan, A. T., Raderer, M., Sedláčková, E., Cadiot, G., Wolin, E. M., Capdevila, J., Wall, L., Rindi, G., Langley, A., Martinez, S., Blumberg, J., Ruszniewski, P., & CLARINET Investigators (2014). Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *The New England journal of medicine*, 371(3), 224–233. <https://doi.org/10.1056/NEJMoa1316158>
24. Michael, M., Garcia-Carbonero, R., Weber, M. M., Lombard-Bohas, C., Toumpanakis, C., & Hicks, R. J. (2017). The Antiproliferative Role of Lanreotide in Controlling Growth of Neuroendocrine Tumors: A Systematic Review. *The oncologist*, 22(3), 272–285. <https://doi.org/10.1634/theoncologist.2016-0305>
25. Arnold, R., Wied, M., & Behr, T. H. (2002). Somatostatin analogues in the treatment of endocrine tumors of the gastrointestinal tract. *Expert opinion on pharmacotherapy*, 3(6), 643–656. <https://doi.org/10.1517/14656566.3.6.643>
26. Lamberts, S. W., van der Lely, A. J., de Herder, W. W., & Hofland, L. J. (1996). Octreotide. *The New England journal of medicine*, 334(4), 246–254. <https://doi.org/10.1056/NEJM199601253340408>
27. Newman, C. B., Melmed, S., Snyder, P. J., Young, W. F., Boyajy, L. D., Levy, R., Stewart, W. N., Klibanski, A., Molitch, M. E., & Gagel, R. F. (1995). Safety and efficacy of long-term octreotide therapy of acromegaly: results of a multicenter trial in 103 patients--a clinical research center study. *The Journal of clinical endocrinology and metabolism*, 80(9), 2768–2775. <https://doi.org/10.1210/jcem.80.9.7673422>
28. Bongiovanni, A., Nicolini, S., Ibrahim, T., Foca, F., Sansovini, M., Di Paolo, A., Grassi, I., Liverani, C., Calabrese, C., Ranallo, N., Matteucci, F., Paganelli, G., & Severi, S. (2022). 177Lu-DOTATATE Efficacy and Safety in Functioning Neuroendocrine Tumors: A Joint Analysis of Phase II Prospective Clinical Trials. *Cancers*, 14(24), 6022. <https://doi.org/10.3390/cancers14246022>

29. De Herder, W. W., Van Schaik, E., Kwekkeboom, D. J., & Feelders, R. A. (2011b). New therapeutic options for metastatic malignant insulinomas. *Clinical Endocrinology*, 75(3), 277–284. <https://doi.org/10.1111/j.1365-2265.2011.04145.x>
30. Strosberg, J., El-Haddad, G., Wolin, E., Hendifar, A., Yao, J., Chasen, B., Mittra, E., Kunz, P. L., Kulke, M. H., Jacene, H., Bushnell, D., O'Dorisio, T. M., Baum, R. P., Kulkarni, H. R., Caplin, M., Lebtahi, R., Hobday, T., Delpassand, E., Van Cutsem, E., Benson, A., ... NETTER-1 Trial Investigators (2017). Phase 3 Trial of ¹⁷⁷Lu-Dotatate for Midgut Neuroendocrine Tumors. *The New England journal of medicine*, 376(2), 125–135. <https://doi.org/10.1056/NEJMoa1607427>
31. Brabander, T., van der Zwan, W. A., Teunissen, J. J. M., Kam, B. L. R., Feelders, R. A., de Herder, W. W., van Eijck, C. H. J., Franssen, G. J. H., Krenning, E. P., & Kwekkeboom, D. J. (2017). Long-Term Efficacy, Survival, and Safety of [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors. *Clinical cancer research : an official journal of the American Association for Cancer Research*, 23(16), 4617–4624. <https://doi.org/10.1158/1078-0432.CCR-16-2743>
32. Cives, M., & Strosberg, J. (2017). Radionuclide Therapy for Neuroendocrine Tumors. *Current oncology reports*, 19(2), 9. <https://doi.org/10.1007/s11912-017-0567-8>
33. Asti, M., Tegoni, M., Farioli, D., Iori, M., Guidotti, C., Cutler, C. S., Mayer, P., Versari, A., & Salvo, D. (2012). Influence of cations on the complexation yield of DOTATATE with yttrium and lutetium: a perspective study for enhancing the 90Y and 177Lu labeling conditions. *Nuclear medicine and biology*, 39(4), 509–517. <https://doi.org/10.1016/j.nucmedbio.2011.10.015>
34. de Araújo, E. B., Caldeira Filho, J. S., Nagamati, L. T., Muramoto, E., Colturato, M. T., Couto, R. M., Pujatti, P. B., Mengatti, J., & Silva, C. P. (2009). A comparative study of 131I and 177Lu labeled somatostatin analogues for therapy of neuroendocrine tumours. *Applied radiation and isotopes : including data, instrumentation and methods for use in agriculture, industry and medicine*, 67(2), 227–233. <https://doi.org/10.1016/j.apradiso.2008.09.009>
35. Cives, M., & Strosberg, J. R. (2017). Treatment Strategies for Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract. *Current Treatment Options in Oncology*, 18(3). <https://doi.org/10.1007/s11864-017-0461-5>
36. Hofland, J., Brabander, T., Verburg, F. A., Feelders, R. A., & De Herder, W. W. (2022). Peptide Receptor Radionuclide Therapy. *The Journal of Clinical Endocrinology and Metabolism*, 107(12), 3199–3208. <https://doi.org/10.1210/clinem/dgac574>
37. Bergsma, H., Konijnenberg, M., Kam, B. L. R., Teunissen, J. J., Kooij, P. P. M., De Herder, W. W. W., Franssen, G. J. H., Van Eijck, C. H., Krenning, E. P., & Kwekkeboom, D. J. (2016). Subacute haematotoxicity after PRRT with 177Lu-DOTA-octreotate: prognostic factors, incidence and course. *European Journal of Nuclear Medicine and Molecular Imaging*, 43(3), 453–463. <https://doi.org/10.1007/s00259-015-3193-4>
38. Bergsma, H., Van Lom, K., Raaijmakers, M. H., Konijnenberg, M. W., Kam, B. B. L., Teunissen, J. J., De Herder, W. W., Krenning, E. P., & Kwekkeboom, D. J. (2018). Persistent Hematologic Dysfunction after Peptide Receptor Radionuclide Therapy with ¹⁷⁷Lu-DOTATATE: Incidence, Course, and Predicting Factors in Patients with Gastroenteropancreatic Neuroendocrine Tumors. *The Journal of Nuclear Medicine*, 59(3), 452–458. <https://doi.org/10.2967/jnumed.117.189712>

39. Kwekkeboom, D. J., de Herder, W. W., Kam, B. L., van Eijck, C. H., van Essen, M., Kooij, P. P., Feelders, R. A., van Aken, M. O., & Krenning, E. P. (2008). Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 26(13), 2124–2130. <https://doi.org/10.1200/JCO.2007.15.2553>
40. Ong, G. S., Henley, D. E., Hurley, D., Turner, J. H., Claringbold, P. G., & Fegan, P. G. (2010). Therapies for the medical management of persistent hypoglycaemia in two cases of inoperable malignant insulinoma. *European journal of endocrinology*, 162(5), 1001–1008. <https://doi.org/10.1530/EJE-09-1010>
41. Zandee, W. T., Brabander, T., Blažević, A., Kam, B. L. R., Teunissen, J. J. M., Feelders, R. A., Hofland, J., & de Herder, W. W. (2019). Symptomatic and Radiological Response to 177Lu-DOTATATE for the Treatment of Functioning Pancreatic Neuroendocrine Tumors. *The Journal of clinical endocrinology and metabolism*, 104(4), 1336–1344. <https://doi.org/10.1210/jc.2018-01991>
42. Kumar, S., Melek, M., & Rohl, P. J. (2022). Case Report: Hypoglycemia Due to Metastatic Insulinoma in Insulin-Dependent Type 2 Diabetes Successfully Treated With 177 Lu-DOTATATE. *Frontiers in Endocrinology*, 13. <https://doi.org/10.3389/fendo.2022.906012>
43. Magalhães, D., Sampaio, I. L., Ferreira, G., Bogalho, P., Martins-Branco, D., Santos, R. L., & Duarte, H. (2019). Peptide receptor radionuclide therapy with 177Lu-DOTA-TATE as a promising treatment of malignant insulinoma: a series of case reports and literature review. *Journal of Endocrinological Investigation*, 42(3), 249–260. <https://doi.org/10.1007/s40618-018-0911-3>

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.

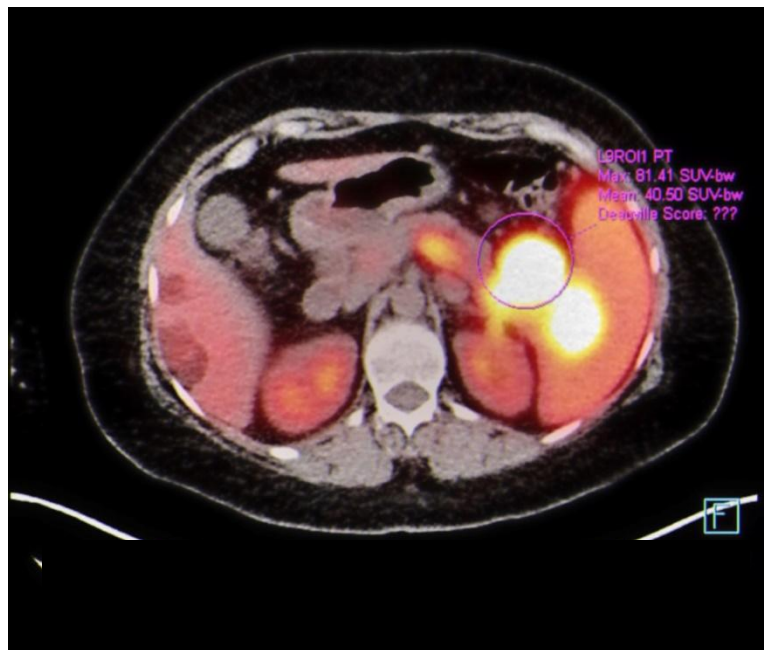


Figure (2):



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.

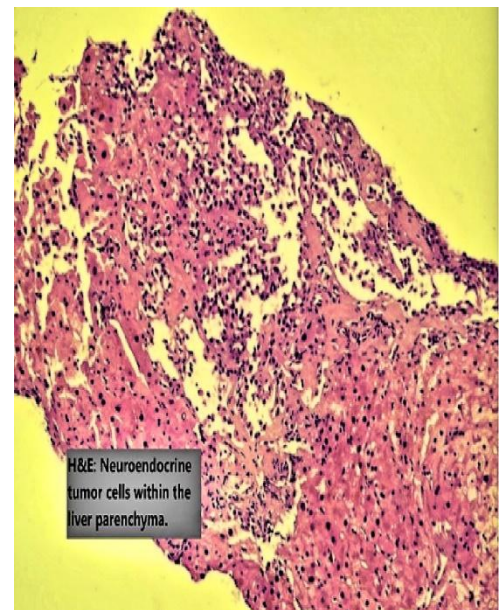


Figure (4):

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

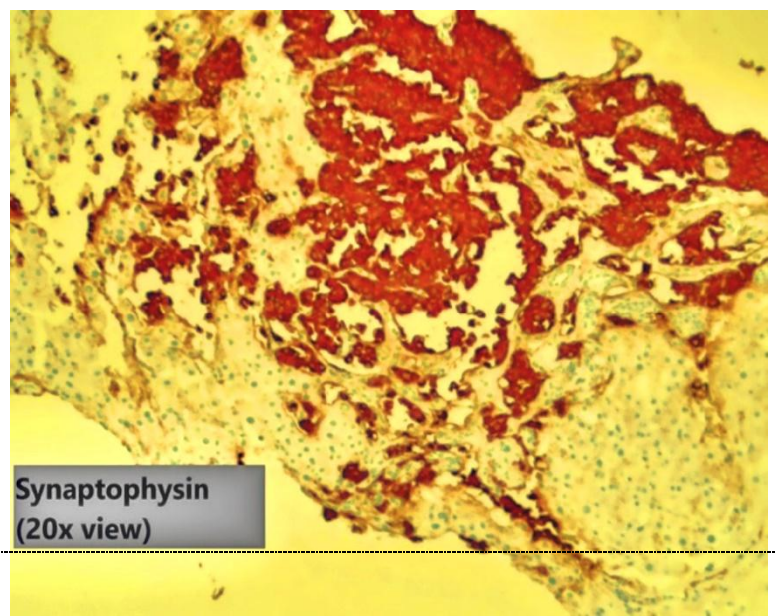


Figure (5):

The figure shows the tumor cells positively stained with chromogranin.

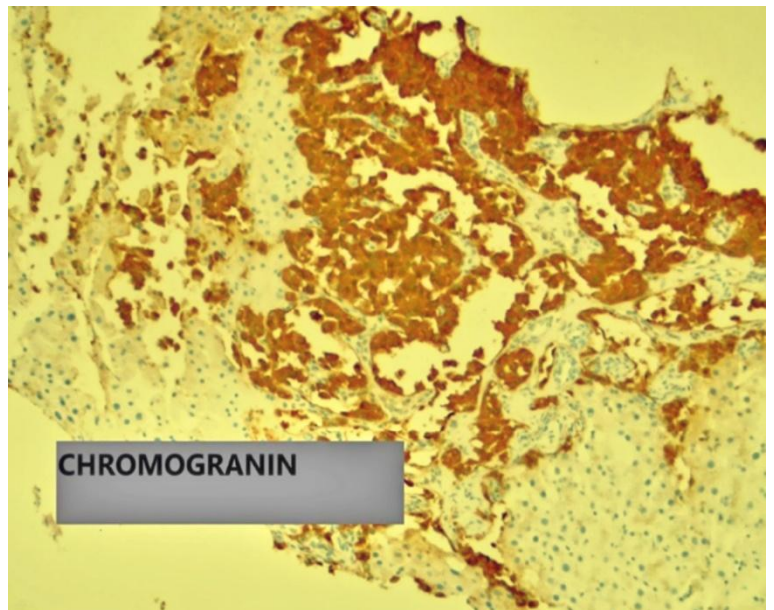
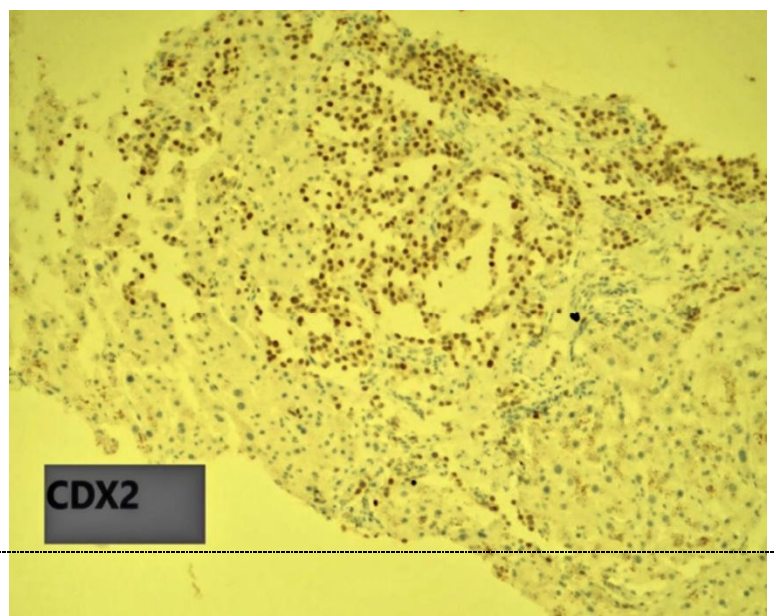


Figure (6):



The tumor cells presented within this figure exhibit CDX2 stain.

Figure (7):

This illustration displays the tumor cells depicting the Ki-67 proliferation index.

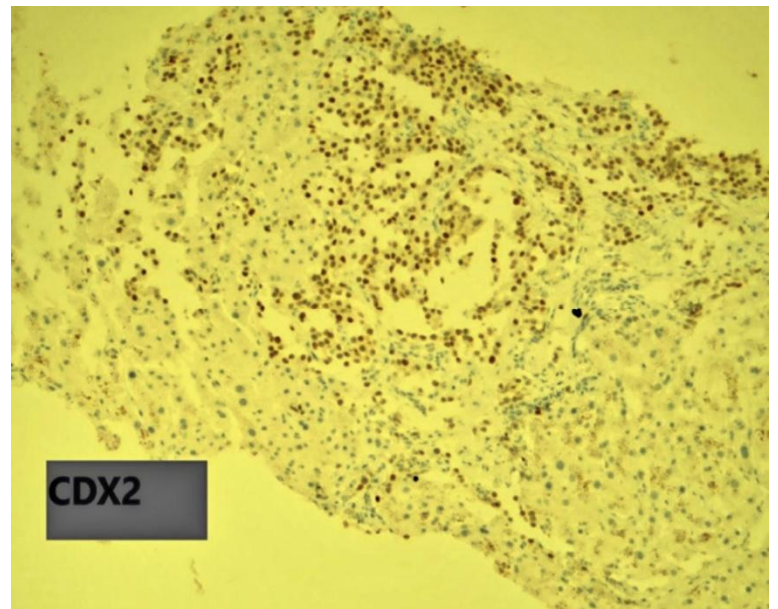
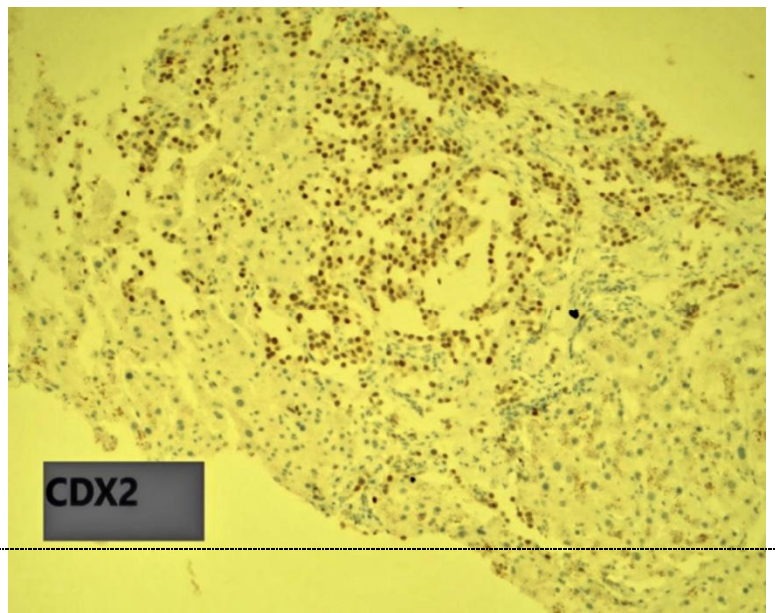


Figure (8):

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.

