JCEM Case Reports, 2024, **2**, luae175
https://doi.org/10.1210/jcemcr/luae175
Advance access publication 27 September 2024
Case Report

Proton Stereotactic Body Radiotherapy for Liver Metastases From Malignant Pancreatic Insulinoma

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Abstract

Insulin-producing pancreatic tumors are a common subtype of neuroendocrine tumor. Standard of care includes surgical resection of the pancreatic tumor and medical management with somatostatin analogs. For patients with metastatic disease, tumor control and hypoglycemic symptom relief can be achieved through surgical resection of the tumor, hepatic artery embolization, radiofrequency ablation, or radioembolization using radioactive isotopes as well as with systemic therapy such as somatostatin analogs and everolimus. We present the case of a 74-year-old male with metastatic insulin-producing pancreatic carcinoma. After a long history of successfully controlling his hypoglycemic episodes post-liver wedge resection, bland embolizations subsequently failed to maintain control of the frequency and severity of his hypoglycemic symptoms. Stereotactic body radiotherapy (SBRT) with protons was used to achieve symptomatic control and led to partial radiographic response with complete resolution of his hypoglycemic episodes. This case demonstrates the potential utility of proton SBRT in metastatic insulinomas.

Key Words: SBRT, radiotherapy, metastatic insulinoma

Introduction

Neuroendocrine tumors (NETs) are a group of heterogenous tumors that can arise from any neuroendocrine tissue within the body. Of these, insulinomas are the most common type of functioning NET, arising from insulin-producing pancreatic islet cells. While typically benign, insulinomas can cause a significant impact on an individual's quality of life due to frequent hypoglycemic events driven by uncontrolled secretion of insulin. Primary management includes surgical resection of the tumor. For patients who are not surgical candidates or who have undetectable primary tumors, medical management using somatostatin analogs, including octreotide and lanreotide, can be effective at controlling the sequelae of insulin excess (1). Inhibitors of the mammalian target of rapamycin (mTOR) such as everolimus have been successfully used to control the hypoglycemia of insulinoma in addition to provide control of tumor growth (2). Ten to 15% of patients develop metastatic disease, with regional lymph nodes and the liver the most common sites of spread (3, 4). Liver-directed therapy targeting these lesions aims to prolong survival and reduce the burden of hypoglycemic episodes. For an individual with a limited number of hepatic lesions, options include surgical resection, percutaneous ablation, or transarterial therapies that include bland embolization, chemoembolization, or radioembolization using radioactive isotopes such as yttrium-90 (5). Focal external beam radiotherapy has demonstrated clear promise in the control of liver metastasis: stereotactic body radiotherapy (SBRT) uses multiple conformal beams to achieve precise targeting of high-dose radiation to target tissue (6). It has become a treatment mainstay for several cancers including lung and prostate. In the liver, SBRT has shown promise in treating both primary disease (7-9) and metastatic lesions from other cancers (8-11). There are several case series demonstrating that SBRT can be effective at achieving local tumor control for NETs (12-16); however, there are limited data on the efficacy of SBRT in achieving control of hormone hypersecretion.

Here we report a case of an individual with a history of metastatic insulinoma with hypoglycemic episodes refractory to traditional treatment who responded well to proton SBRT.

Case Presentation

At original diagnosis, a man in his 50s presented with multiple episodes characterized by neurocognitive dysfunction and was eventually found to have hyperinsulinemic hypoglycemia accompanied by a tumor in the distal pancreas and elevated insulin levels. He underwent a distal pancreatectomy and splenectomy with pathology demonstrating a 3.7 cm neuroendocrine islet cell tumor in the distal pancreas (positive for chromogranin and synaptophysin, negative for progesterone, >10 mitoses/10 high-powered field), with focal extension into the peripancreatic fat but no lymph node involvement. Approximately 3 years after distal pancreatectomy, he

Received: 5 August 2024. **Editorial Decision:** 13 September 2024. **Corrected and Typeset:** 27 September 2024

developed recurrent hypoglycemic symptoms; hepatic metastases were detected on computed tomography scan and subsequently confirmed to be of neuroendocrine origin by fine needle aspiration. This led him to undergo subsegmental resection and radiofrequency ablation of 5 hepatic lesions. At 7 years postdiagnosis, there was evidence of symptomatic and radiographic progression leading him to receive transarterial radioembolization with yttrium-90 to the right hepatic artery. This provided symptomatic control for approximately 3 years. Following this, from 9 to 15 years postdiagnosis, his hypoglycemic symptoms were controlled by multiple bland embolization procedures to a growing right hepatic lobe lesion that was continuing to cause hypoglycemic episodes. Each of these provided excellent tumor and symptom control. At 15 years postdiagnosis, these procedures started to have diminishing benefits for his hypoglycemic episodes and long-acting repeatable octreotide was started. In combination with the octreotide, he continued receiving bland embolization procedures for extra control of his hypoglycemic episodes as needed. An attempt was made to increase symptom control using everolimus at 18 years postdiagnosis; however, this was halted secondary to an episode of angioedema and pulmonary edema. At the time of presentation to the radiation oncology clinic (18 years postdiagnosis), his most recent embolization failed to reduce the frequency or severity of his hypoglycemic episodes, necessitating discussion of alternative therapeutic modalities to address these symptoms.

At this time, he was having multiple hypoglycemic episodes per day, requiring him to wear a blood glucose monitor, and he was unable to drive. These episodes also led to frequent consumption of high glycemic index foods to suppress and prevent these symptoms, causing the patient to gain weight. There were no outside records of the patient's serum chromogranin A levels at baseline. At one point after multiple lines of therapy 10 years after initial diagnosis, it was measured and was not elevated at 75 ng/mL (3600 nmol/L) (normal reference range of <95 ng/mL; < 4560 nmol/L), so this was not followed over the course of subsequent therapies.

Diagnostic Assessment

Positron emission tomography/computed tomography and magnetic resonance imaging (MRI) revealed 2 lesions of concern in the right lobe and a smaller 1 on the dome of the liver (Fig. 1). The right lobe lesion had been the target of the most recent bland embolization but still showed evidence of disease.

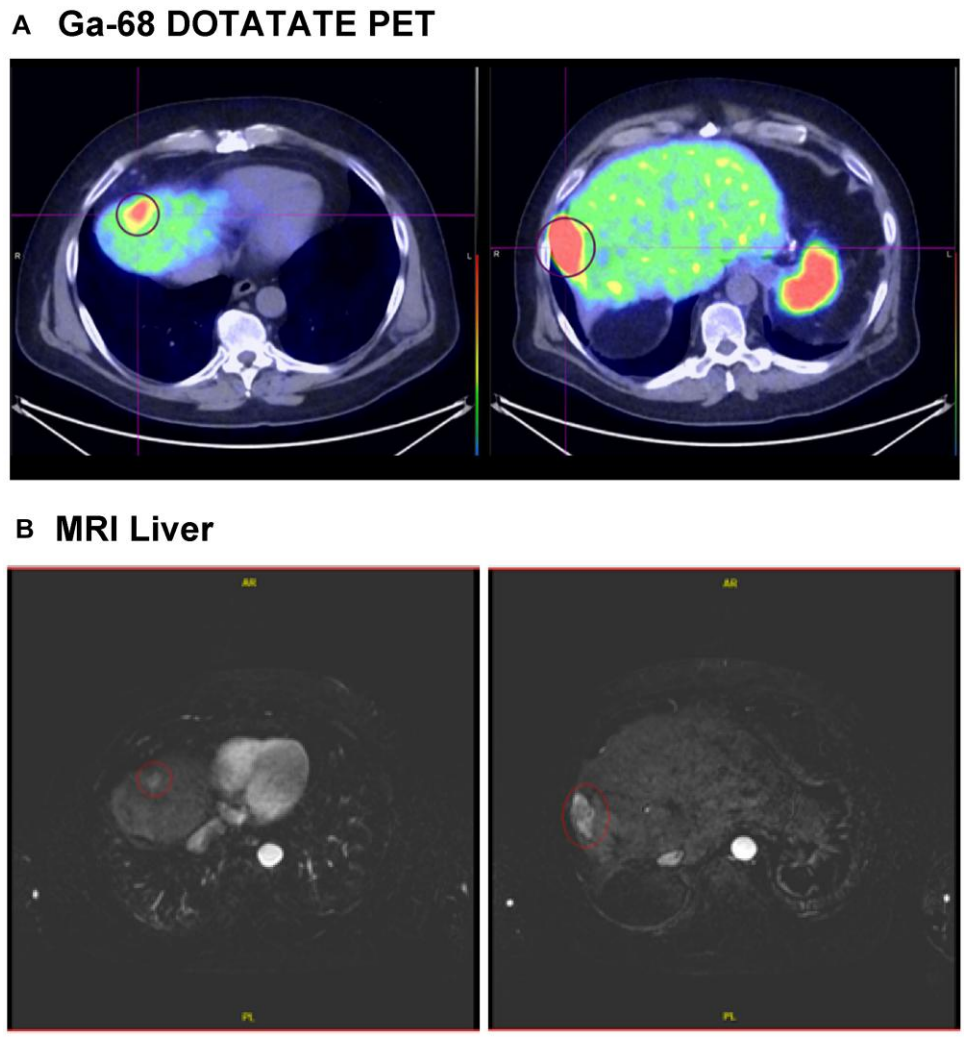

Figure 1. Imaging at time of consultation. (A) Ga-68 DOTATATE positron emission tomography. (B) Magnetic resonance imaging liver.

Treatment

Proton SBRT consisting of 50 Gy in 5 fractions delivered every other day was recommended (Fig. 2). The pateint experienced no acute toxicities other than fatigue, which was managed with rest. During the course of treatment, he continued to have multiple hypoglycemic episodes per day, which were managed with dietary intake and constant blood glucose monitoring.

Outcome and Follow-up

After completing his prescribed SBRT course, the patient's hypoglycemic episodes continued for about 1 week. After this, his hypoglycemic episodes became less frequent and less severe, eventually completely resolving within 3 to 4 months post-SBRT. Based on this, the decision was made to discontinue his long-acting repeatable octreotide, and this did not lead to recurrence of symptoms. Follow-up imaging at 4 months post-SBRT revealed a slight increase in the anterior right hepatic dome lesion and an increase in the perihepatic nodularity (Fig. 3A). At his 9-month month follow-up, somatostatin receptor 2 (Ga-68 DOTATATE) positron emission tomography/MRI imaging revealed a partial radiographic response (Fig. 3B). At 15 months post-SBRT, MRI of the abdomen/liver demonstrated that both lesions remained stable with no new sites of disease. The patient denied any hypoglycemic episodes in the intervening time, and the decision was made to continue observation without resuming any systemic therapy.

Discussion

Here we describe a patient who presented with poorly controlled hypoglycemia in the context of a metastatic insulinoma. At presentation, bland embolizations and systemic therapy had ceased to provide symptomatic relief or were not tolerated, necessitating an alternative treatment approach.

For patients with metastatic insulinomas, therapy is directed at reducing the frequency and burden of symptomatic episodes. Several medical therapies exist for this, as highlighted by our case. First, somatostatin analogs such as octreotide and lanreotide have strong affinity for the somatostatin receptor 2 and can provide effective symptom and tumor control for patients. However, a significant number of patients do not respond to these therapies, with current estimates around 40% of all NETs (17, 18). These nonresponders tend to be enriched for insulin- and gastrin-secreting NETs. Additionally, a

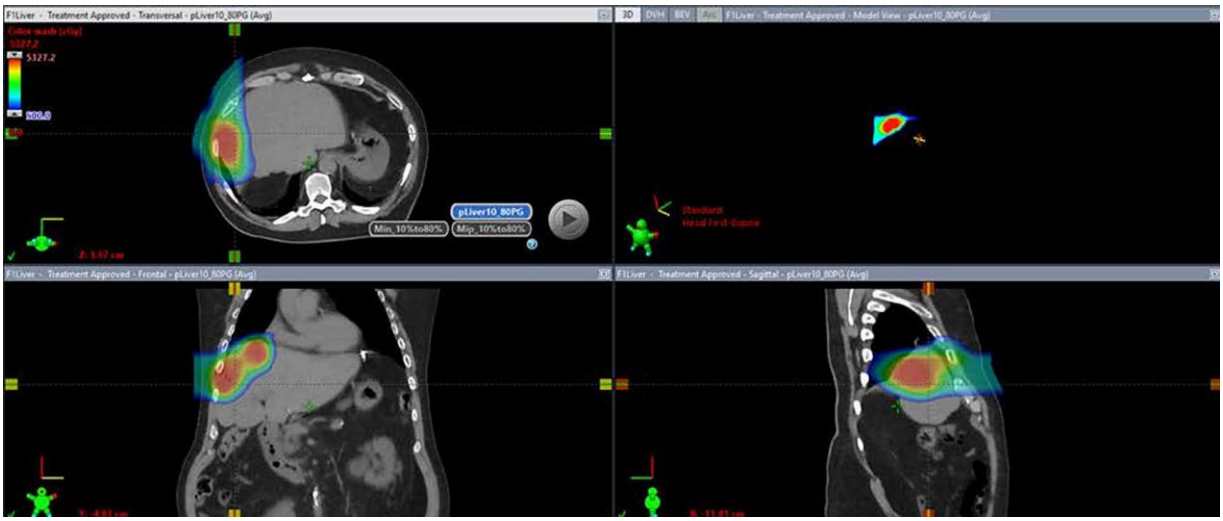

Figure 2. Proton stereotactic body radiotherapy plan.

Figure 3. Follow-up imaging at 4, 9, and 15 months post-stereotactic body radiotherapy.

number of advanced therapies are being developed for patients with metastatic insulinomas including several receptor tyrosine kinase and mTOR inhibitors (1). While these advanced therapies hold potential promise for many patients, they carry risks associated with their use. Some of the most significant side effects of everolimus include stomatitis, pneumonitis, thrombocytopenia, diarrhea, and anemia (1). Our patient developed an angioedema-like response after initiating everolimus, which prevented their continued use. While uncommon, it is recognized that individuals taking mTOR inhibitors are at increased risk of developing angioedema when combined with an angiotensin-converting enzyme inhibitor. Current estimates place the incidence of angioedema around 5% to 6% in patients receiving both drugs compared to 1% to 2% of individuals taking either drug alone (19, 20). Of note, our patient was taking an angiotensin-converting enzyme inhibitor (enalaparil). For sunitinib, significant side effects include neutropenia, diarrhea, hypertension, and thrombocytopenia (1). Our patient had a history of hypertension and stage 2 chronic kidney disease, disfavoring the use of sunitinib.

Based on the patient's increasing symptoms, both SBRT and peptide receptor radionuclide therapy were discussed as potential management options at the time of consult with radiation oncology. Given imaging studies demonstrated that his disease was localized to only 2 foci that could be treated with ablative radiotherapy doses, and his excellent long-term responses to prior focal therapies, SBRT was favored as the initial approach in this case—reserving peptide receptor radionuclide therapy for if he were to progress with more foci of disease or if SBRT were to fail to control his disease. Conventional approaches for delivering radiation using external beams have demonstrated utility in controlling and eliminating pancreatic NETs (21-24). In several clinical studies, SBRT has been demonstrated to be effective for the treatment of metastatic lesions in the liver with no reported cases of radiation-induced liver disease following completion of SBRT (8-11). However, the data on metastatic pancreatic NETs are much less defined (12, 24-26).

Overall, our case lines up well with the reported literature. The treatment course was delivered as planned consisting of 50 Gy in 5 fractions, which is well below the limits established by previous dose-escalation trials for metastatic hepatic masse. There are 2 reported cases where SBRT was specifically used to treat metastatic insulinomas. The first was an individual treated with stereotactic radiosurgery (CyberKnife, 25 Gy in 1 fraction) (25), and the second was an individual treated with SBRT (45 Gy in 5 fractions) (12). There was also one case where an individual was treated with SBRT (30 Gy in 3 fractions) to 2 pancreatic insulin-secreting NETs (12). In addition to showing radiographic evidence of tumor response, each of these individuals had sustained increases in their blood glucose levels allowing them to maintain glycemic control off medical therapy. This aligns with our experience here where our patient has continued to maintain proper glycemic control with no hypoglycemic episodes reported in the absence of systemic therapy. These data highlight the potential utility for SBRT in both local and symptomatic control of insulin-secreting NETs. Based on these clinical observations, it will be of interest to determine whether symptom control is purely a function of the antitumor activity of SBRT or whether there are specific radiobiological effects on pancreatic NETs that decrease their insulin secretion.

There are limited other instances where radiation has shown promise in decreasing symptoms from hormonal overproduction in addition to providing local control of the tumor. One such example is the treatment of secretory pituitary adenomas (27, 28). Like insulinomas, these typically benign tumors can cause symptoms secondary to the secretion of pituitary hormones such as ACTH, GH, or prolactin. Available data suggest that radiation is effective at both providing local control of these tumors and reducing hormonal production. Of note, there is some evidence that stereotactic radiosurgery induces a more rapid normalization in hormone levels compared to fractionated radiotherapy (29). However, this data is mostly in individuals with GH-secreting adenomas. Across all types, radiotherapy appears to be most effective at reducing hormonal production from ACTH-secreting and GH-secreting adenomas, whereas prolactin-secreting adenomas do not tend to show robust responses in hormone secretion (27). The clinical benefit from decreased hormone production is typically seen after 1 to 2 months. This lines up well with our patient where hypoglycemic symptom improvement was seen after 1 month and octreotide independence was achieved 4 months after SBRT and with other reported insulinoma cases where blood glucose normalization occurred 1 to 2 months after radiotherapy (12, 25).

In conclusion, we present the case of an individual with a metastatic insulinoma who responded well to SBRT, achieving independence from somatostatin analogs with complete abrogation of his hypoglycemic episodes. This case supports future investigation of SBRT as a tool for achieving disease and symptom control for patients with metastatic insulinomas.

Learning Points

- SBRT can be an effective tool for decreasing hypoglycemic symptoms in patients with oligometastatic insulinomas.
- Improvement in symptomatic hypoglycemic episodes occurred within 1 week, with full resolution by 3 to 4 months post-SBRT.
- At 20 months post-SBRT, the patient continued to be free from hypoglycemic episodes, and the treated lesions remained radiographically stable.

Acknowledgments

The authors would like to thank the patient and all members of their care team.

Contributors

All authors made individual contributions to authorship. J.K., D.E., and C.C. wrote and edited the initial draft. C.C. and T.H. were involved in the diagnosis, management, and treatment of this patient. J.K., D.E., K.J., K.M., T.H., and C.C. were involved in the editing, literature review, and discussion/introduction section of the final draft. All authors reviewed and approved the final draft.

Funding

No public or commercial funding directly funded this work. J.K. was supported by the National Institutes of Health (T32GM145408).

Disclosures

T.R.H. receives research support from Thermo Fisher Scientific, Advanced Accelerator Applications (a Novartis company), Camurus, Crinetics, ITM Isotopen Technologien Muenchen, and Perspective Therapeutics. Additionally, T.R.H. has served in a consultancy/advisory board capacity with Exelixis, TerSera, Curium, Ipsen, Novartis, ITM Isotopen Technologien Muenchen, Crinetics, Perspective Therapeutics, Camurus, and Abdera Therapeutics. All other authors have no disclosures to report.

Informed Patient Consent for Publication

Signed informed consent could not be obtained from the patient or a proxy but has been approved by the treating institution.

Data Availability Statement

Original data generated and analyzed during this study are included in the published article.

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