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Case Report

Radiofrequency Ablation as a Primary Therapy for Benign Functioning Insulinoma

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ABSTRACT

Objective: Insulinomas are rare, life-threatening pancreatic neuroendocrine tumors. Surgical removal continues to be the treatment of choice, yet it is associated with considerable risk of morbidity. Here, we describe our patient with insulinoma who was successfully treated with radiofrequency ablation.
Methods: The patient was a 56-year-old man with no history of diabetes mellitus. He presented with recurrent episodes of transient ischemic attacks and stroke over the last 3 years. Some changes in his behavior and memory were noticed by family members. During his hospital stay for the second transient ischemic attack, frequent hypoglycemia was documented, which was asymptomatic. Insulinoma was confirmed biochemically. Radiological findings were also compatible with pancreatic neuroendocrine tumor. Treatment modalities were explained to the patient. However, he strongly refused surgery. Meanwhile, he was admitted because of a stroke and concurrent hypoglycemia again. In view of his refusal of the surgical treatment and due to his presentation with acute stroke and high-risk status for surgery, radiofrequency ablation was finalized.
Results: Radiofrequency ablation of the pancreatic tumor using 40.75 Gy over fractions was performed with a favorable outcome. The patient has achieved biochemical normalization and remained euglycemic during his follow- up. Computed tomography scan of the abdomen during follow-up showed a mild regression of the size of the tumor.
Conclusion: This report shows a treatment challenge that required the use of an alternative treatment option other than the standard of care. It highlights the evolving evidence of radiofrequency as a therapeutic modality for patients with insulinoma.

Introduction

Insulinomas are rare, insulin-secreting pancreatic neuroendocrine tumors (pNETs) with an annual incidence of 4 cases per million per year.[1] Most insulinomas are sporadic, solitary, and benign, yet associated with life-threatening hypoglycemia due to autonomous insulin secretion.[2] Approximately 10% of insulinomas are malignant, and 4% to 7% are associated with multiple endocrine neoplasia syndrome type I.[3] The diagnosis of insulinoma is usually delayed because of its deceptive, disguising, nonspecific symptoms that mimic other disorders such as neuropsychiatric illness.[4,5]

The Whipple's triad is the clinical hallmark of hypoglycemia and is the cardinal symptom in patients with insulinoma. It consists of (1) documented (measured) low blood glucose, (2) in the presence of clinical symptoms consistent with hypoglycemia, (3) that are relieved after plasma glucose level is raised.[6] Once endogenous hyperinsulinemic hypoglycemia has been confirmed by the supervised prolonged fasting test, localization studies can be carried out.

Conventional imaging techniques such as contrast enhanced computed tomography (CT) and magnetic resonance imaging do not always lead to localizing the culprit pNET, due to its often small size. Endoscopic ultrasound, selective angiography, and selective pancreatic arterial calcium stimulation are invasive approaches

Abbreviations: CT, computed tomography; pNET, pancreatic neuroendocrine tumors; RFA, radiofrequency ablation; TIA, transient ischemic attacks.

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Table 1
Laboratory Investigation during 72-hour Supervised Test

Feature	Patient's value	Reference range
Random blood glucose (mmol/L)	2.04	4.0-5.6
Serum Insulin (mU/L)	68.9	3-13
Serum C-peptide (μg/L)	4.08	1.0-3.1

that are often necessary.[7] The octreotide scan has low sensitivity in the diagnosis of insulinoma, while ^{68}Ga-DOTATATE positron emission tomography/CT identifies most insulinomas.[8] Taking the advantage of overexpressed glucagon-like peptide-1 receptors in benign insulinomas, glucagon-like peptide-1 receptor-based imaging with gallium-68 labeled exendin-4 positron emission tomography/CT or single-photon emission CT/CT is also an emerging, promising new modality of localization in small benign insulinomas.[9]

Surgical removal continues to be the treatment of choice for such benign lesions with a high cure rate. However, surgery is associated with a considerable risk of morbidity and mortality.[10] Medical treatment or trans-catheter arterial embolization are therapeutic options if surgery is not feasible or refused.[11] A new treatment modality that has recently evolved but is not yet widely used is radiofrequency ablation (RFA). Several cases of its successful use in the treatment of patients with insulinoma have been reported recently.[12]

Here, we describe a patient with benign solitary insulinoma who presented initially with recurrent transient ischemic attacks (TIA) and strokes, which were successfully treated with RFA while surgery was not feasible due to surgical high-risk status and the patient's refusal.

Case Report

A 56-year-old male with a history of hypertension, who survived lymphoma 36 years back, presented with recurrent episodes of TIA and stroke over the preceding 3 years. His first episode of TIA was 3 years ago, when he had headache, right-sided weakness, and dysarthria after a long car ride, with spontaneous recovery of his symptoms after 5 hours. He was managed in the emergency room and a CT scan of his brain was normal. The laboratory results from that visit included a random blood glucose of 3.6 mmol/L, which was corrected with intravenous dextrose, and he was discharged home on aspirin on the same day.

He subsequently experienced another episode of TIA, 18 months following the initial one. He had numbness of the right side of the face and body, which resolved spontaneously after an hour. He was hospitalized for further workup. CT scan of the brain was normal. During his hospital stay, several episodes of asymptomatic hypoglycemia were documented during his sleep, early mornings, and between meals. He denied any palpitation, sweating, blurred vision, seizures, or loss of consciousness. He did not notice any change in his weight. An alteration in his behavior and memory was noticed by his family members. However, his behavioral and cognitive function was not assessed by a validated mental status examination tool. He denied taking any prescribed medications, other than his antihypertensive medication, or over-the-counter supplements. He has no personal or family history of diabetes.

Shortly after hospitalization, a prolonged supervised fasting test was performed. After 12 hours of fasting, his blood glucose dropped to 1.9 mmol/L without any symptoms and was promptly managed with intravenous dextrose. Laboratory studies demonstrated a low plasma glucose level with inappropriately elevated plasma levels of insulin and C-peptide (Table 1). Serum sulfonylurea screening test was negative. Based on the laboratory findings, insulinoma was confirmed biochemically. He had a CT scan of the abdomen (Fig. 1 *A*), which revealed an enhancing lesion at the uncinate process of the pancreas measuring 3.5 × 2.5 cm and no definitive intra-abdominal metastatic lesions. An magnetic resonance imaging of the abdomen (Fig. 2) revealed a 3.2 × 2.5 cm, well-circumscribed hypervascular lesion at the uncinate process of the pancreas, compatible with a neuroendocrine tumor; no intraabdominal metastatic lesions were seen. Basal and stimulated serum cortisol level, thyroid function profile, and calcium, parathyroid hormone, prolactin, and adrenocorticotropic hormone levels were all within normal range. Hence, the possibility of multiple endocrine neoplasia syndrome type I was excluded. Surgical enucleation was explained and offered to the patient, who was fully informed about the potential risks and benefits. However, he strongly refused surgery. He was educated about taking frequent meals and snacks along with the monitoring of blood glucose at home. Diazoxide was prescribed and a follow-up appointment with the treating team was scheduled.

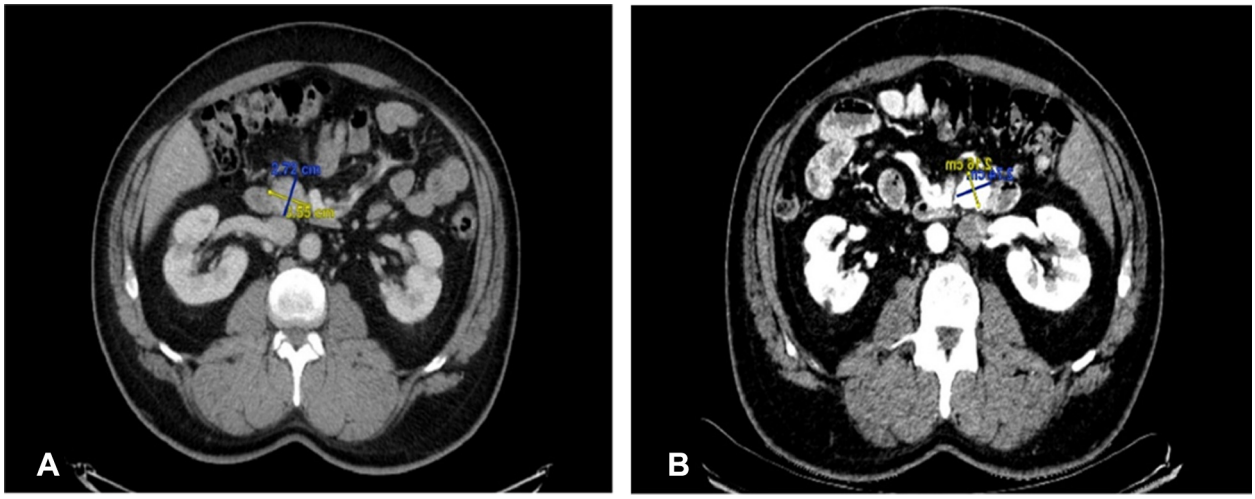

Fig. 1. *A*, Computed tomography of the abdomen upon diagnosis showing an enhancing lesion at the uncinate process of the pancreas measuring 3.5 × 2.5 cm and no definitive intraabdominal metastatic lesions. *B*, Computed tomography of the abdomen 2 months after the radiofrequency ablation therapy showing an interval decrease in the size of the previously described enhanced uncinate process mass and measuring 2.9 × 2.6 cm. No evidence of new lesions or distance metastasis.

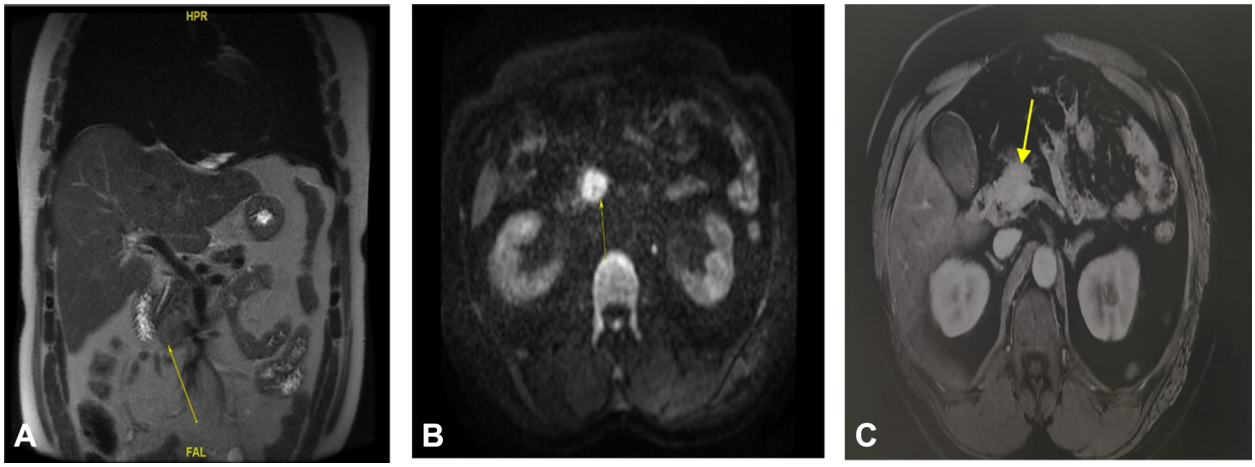

Fig. 2. Magnetic resonance imaging upon diagnosis *A*, T2 image. *B*, Diffusion image. *C*, post-contrast image showing a 3.2 × 2.5-cm well-circumscribed hypervascular lesion (arrow) centered at the uncinate process of the pancreas, showing mild washout on delayed post-contrast images, with corresponding intermediate bright signal intensity on T2-weighted image and diffuse restriction.

Four months after, he had an acute ischemic stroke that manifested as left side facial deviation, right upper limb weakness, and expressive aphasia. His CT and magnetic resonance imaging brain scans confirmed a left middle cerebral artery infarction. At this point, the patient was still refusing surgical treatment for the insulinoma, and his surgical risk was also considered high due to the recent acute stroke. For this reason, RFA therapy was offered. The patient was given details about the RFA efficacy and potential complications (duodenitis, duodenal ulcer, and fistula). A shared decision with the patient was made, and RFA was carried out using 40.75 GY over 4 fractions. The procedure was well tolerated by the patient with a favorable outcome.

The patient achieved biochemical normalization and remained euglycemic shortly after the RFA, which was shown by his blood glucose readings obtained at home in the first 24 hours after the procedure (ranging between 100-136 mg/dL); he sustained the response at the follow-up period of up to 9 months at the time of writing this report. Reversal of his behavioral and memory changes was recognized by his family members. A CT scan of the abdomen (Fig. 1 *B*) at 2 months after the RFA therapy showed a mild regression of the size of the tumor to 2.9 × 2.6 cm, with no evidence of new lesions or distant metastasis. He has remained under close follow-up at the neuroendocrine clinic.

Discussion

Our report describes a patient with solitary, benign insulinoma who presented with recurrent TIAs, stroke, and behavioral changes, which was managed successfully with RFA.

Hypoglycemia is one of the metabolic abnormalities that mimics TIA and stroke and needs to be excluded in cases of clinical suspicion of TIA or stroke.[13] Also, it is well known that hypoglycemia can cause hemiparesis and aphasia.[14] The main pathophysiology is not well understood; however, ischemia as a consequence of vasospasm and failure of blood flow autoregulation has been hypothesized.[15] Cognitive impairment in the cases of severe hypoglycemia has also been reported in several cases.[4,16] In our patient, we are not absolutely certain whether the TIA and stroke episodes were hypoglycemia mimickers, consequences of real hypoglycemia, or independent. However, we were certain about the CT brain findings, which confirmed a diagnosis of acute stroke in one of the episodes.

The diagnostic delay in patients with insulinoma is unchanged, despite the improved diagnostic tools.[17] Results of a retrospective study, published by Dinget al,[4] revealed that among 42 patients with insulinoma, more than half presented with neuropsychiatric symptoms, and most of them were not diagnosed correctly until 12 months after the consultation. Delay in diagnosis in similar patients with insulinoma could be due to several factors such as insulin secretion by the insulinoma in bursts, which causes temporary blood glucose fluctuations; the unawareness about the associated hypoglycemia due to chronic recurrent hypoglycemia; the fact that insulinomas are usually small, solitary tumors, which can be missed by conventional radiological investigation; and the similarity in presentation to many common neurologic and psychiatric diseases.

The treatment aim in patients with insulinoma is resolution of hypoglycemia by abating the hormonal hypersecretion through inducing necrosis and death of the large majority of the tumor cells without the need to ablate the tumor completely due to its very low malignant potential. Therapeutic strategies for insulinoma include surgical resection, medical treatment, and ablative therapies. Surgical resection or enucleation has always been the first line treatment modality with a high cure rate; however, these are associated with significant morbidity, with pancreatic fistula being the most common postoperative complication.[18] In patients who refuse surgery or who are at high surgical risk, less invasive alternative therapeutic interventions are warranted.

In 2009, Limmer et al[19] described the first patient with insulinoma who was successfully treated with RFA. Several reports have since been published about patients with insulinoma with complete symptomatic regression after treatment with transcutaneous or laparoscopically RFA, high intensity focused ultrasound ablation, ultrasound assisted alcohol ablation, or selective chemoembolization, with no reported side effects.[13,14,20] However, the follow-up period for these patients is generally short, ranging from 5 weeks to 9 months. Our patient had complete resolution of hypoglycemia within 24 hours after the RFA, as evidenced by his blood glucose readings obtained at home. This biochemical response shortly after RFA is an important marker to assess the successful response to the RFA before the radiological response. Table 2 shows a review of the literature for reports of 10 patients with insulinoma who were treated with RFA.[21–25] Oleinikov et al[20] studied the feasibility, safety, and efficacy of ultrasound guided RFA in 18 patients with pNET (7 patients with insulinomas and 11 nonfunctioning pNET patients). Six out of the 7 patients with

Table 2
Summary of 10 Patients with Insulinoma who had Radiofrequency Ablation Therapy

Reference	Gender	Age (y)	Clinical presentation	Durations of symptoms before diagnosis (mo)	Tumor location	Tumor size (mm)	Technique of ablation	Postoperative complications	Follow-up (mo)	Recurrence	Result
Yao[12]	Female	44	episodic hypoglycemic symptoms	48	Tail	18 × 17	Laparoscopic	No	9	No	Complete ablation
Yao[12]	Female	65	episodic hypoglycemic symptoms	36	Neck of pancreas	15	Laparoscopic	No	43	No	Complete ablation
Limmera[19]	Female	80	Episodes of severe hypoglycemia Symptoms	…	Tail	15	Percutaneous puncture	No	7	No	Complete ablation
Akhlaghpoor[21]	Male	48	Recurrent dizziness. Hunger, perspiration, and nervousness	…	Head	12	Percutaneous puncture	No	36	No	Complete ablation
Procházka[22]	Female	75	Episodes of hypoglycemia symptoms	…	Body	15	Laparoscopic	Transient hyperglycemia	3	No	Complete ablation
Waung[23]	Female	70	Recurrent episodes of dizziness	18	Uncinate process	18	EUS	No	10	No	Complete ablation
Lakhtakia[24]	Male	42	Recurrent episodes of seizures	8	Body	14 × 12	EUS	No	12	No	Complete ablation
Lakhtakia[24]	Male	41	Hypoglycemia with frequent eating and weight gain	12	Head	17 × 12	EUS	No	12	No	Complete ablation
Lakhtakia[24]	Male	52	Recurrent episodes of syncope	24	Head, body, tail	22 × 19	EUS	No	11	No	Complete ablation
Bas-Cutrina[25]	Female	63	Periodic hypoglycemic symptoms		Body	9 × 10	EUS	No	10	No	Complete ablation

EUS = endoscopic ultrasound.

insulinomas refused surgery and preferred RFA. Their tumor sizes ranged from 12 to 19 mm and their ages ranged between 28 to 73 years old. All 7 patients with insulinomas exhibited complete relief of hypoglycemia-related symptoms, and normalization of glucose levels was observed within around an hour after the procedure. It has been shown that if performed by an experienced doctor, RFA can be done safely. However, RFA of the pancreas and especially the head poses a risk of puncturing and thermal injury to the adjacent critical structures. A special consideration has to be taken for lesions adjacent to the main pancreatic duct, in which RFA in some centers is contraindicated because it carries a higher risk of complications.[26] The RadioFrequency Ablation for the Treatment Pancreatic NeuroEndocrine Neoplasms trial (ClinicalTrial.gov identifier NCT03834701) is a new multicenter trial, held to evaluate the possibility and the safety of RFA in treating pNET, and it might provide further insights regarding the safety and the efficacy of this technique.

Conclusion

This report shows a treatment challenge that required the use of an alternative treatment option other than the standard of care in managing a patient with benign insulinoma. Successful treatment was achieved with the use of RFA rather than surgery. This report highlights the evolving evidence of RFA being a potential safe, feasible therapeutic modality or even as an alternative to surgery in selected patients with benign insulinoma. Because of the rarity of this tumor and the low rate of therapeutic application of RFA in similar patients, the role of this treatment modality has not been extensively studied. Larger, multicenter studies involving larger numbers of patients with longer follow-up periods are needed to fill in the gaps about the long-term outcomes and efficacy of RFA as a curative alternative treatment to surgery in patients with insulinoma.

Disclosure

The authors have no multiplicity of interest to disclose.

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