Case Report

Successful Long-Term Medical Management of Unresectable Insulinomas

Andrew J. Spiro Mohamed K.M. Shakir Thanh D. Hoang

Department of Endocrinology, Walter Reed National Military Medical Center,
Bethesda, MD, USA

Keywords

Insulinoma · Metastatic disease · Medical management

Abstract

In this paper, we present two patients with unresectable insulinomas and a literature review. Patient 1: A 58-year-old woman was diagnosed at age 42, with an insulinoma in the pancreatic tail and hepatic metastasis. She underwent distal pancreatectomy, splenectomy, hepatic wedge resection, and chemoembolization, with resolution of her symptoms. By age 48, her symptoms returned, with new hepatic metastasis. She started long-acting octreotide, with subsequent resolution of her symptoms. She has since had an unremarkable clinical course. Patient 2: A 48-year-old female was diagnosed at age 37. Numerous imaging modalities and two exploratory surgeries did not localize a mass. A distal pancreatectomy did not resolve her symptoms. She tried several medications before her symptoms were finally controlled with low-dose prednisone. She has continued prednisone and diazoxide treatment for the past decade, which controls her symptoms, along with diet modification. In conclusion, while prednisone is not standard therapy, it can control symptoms in patients with unresectable insulinoma. Providers should be aware of available and emerging medical options. Patients with unresectable insulinomas will likely have better long-term survival rates than those quoted in historical literature. Additional studies are needed to elucidate survival rate and the long-term efficacy of medical therapies.

© 2020 The Author(s)
Published by S. Karger AG, Basel

Introduction

Insulinomas are functional pancreatic neuroendocrine tumors (pNETs), derived from insulin-secreting β -cells of the pancreas. Estimated incidence is 1–4 new cases per million persons annually [1, 2]. The majority are benign, solitary tumors, less than 2 cm in diameter.

Thanh D. Hoang
Division of Endocrinology, Department of Medicine
Walter Reed National Military Medical Center
8901 Wisconsin Ave, Bethesda, MD 20889 (USA)
tdhdthanh@gmail.com

Fig. 1. Insulinoma metastasizing to the liver (Patient 1).

Multiple tumors present in 5–10% of patients, typically associated with multiple endocrine neoplasia type 1 [1]. Patients may demonstrate neuroglycopenic symptoms of confusion, visual disturbances, behavioral changes, coma, or seizure. Hypoglycemia can cause catecholamine surge, producing adrenergic symptoms of diaphoresis, tremors, and palpitations [2]. Diagnosis is assisted by the presence of Whipple's triad: neuroglycopenic symptoms, plasma glucose <50 mg/dL, relief of symptoms with administration of glucose. The gold standard for diagnosis is 72-hour monitored fast with interval measurements of plasma glucose, insulin, C-peptide, and proinsulin [1, 2]. Surgical resection is the treatment of choice for most patients and the only method of cure. Surgical cure is not possible with unresectable metastatic disease, unlocalizable disease, or contraindications to surgery [1]. Approximately 4–14% of insulinomas are malignant, invading adjacent lymph nodes and tissue, or metastasizing to the liver [3]. Tumor localization can be difficult and 13% of surgical patients undergo re-exploration [2]. We present two patients for whom surgery was not curative and whose symptoms have been well controlled with medical therapy for over 10 years.

Methods

We present the clinical presentation of two patients with unresectable insulinomas who have been successfully managed with medical therapy and performed a literature review.

Case Reports

Patient 1

A 58-year-old woman presented at age 42 with syncope and blood glucose measuring <30 mg/dL. A 72-hour fast demonstrated blood glucose of 46 mg/dL, insulin of 50 mIU/mL (2.6–24.6), and C-peptide of 7.0 ng/mL (1.1–4.4). Her symptoms were managed with frequent small meals. CT showed a 2.4-cm lesion in the pancreas tail. MRI showed two metastatic lesions in the right hepatic lobe. She underwent distal pancreatectomy, splenectomy, and hepatic wedge resection, with radiofrequency ablation of liver metastases. Follow-up CT showed two new lesions in the liver and she underwent chemoembolization with resolution of her symptoms. Symptoms returned by age 48, with MRI showing new lesions throughout the liver (Fig. 1). She was started octreotide 20 mg IM monthly, and her symptoms resolved soon afterward. Since then, she has had stable annual imaging via MRI and well-controlled symptoms.

Table 1. Medication trials of Patient 2

Regimen	Result
Verapamil 80 mg TID	Continued symptoms
Verapamil 80 mg TID, diazoxide 50 mg TID	Continued symptoms
Octreotide 50 µg BID	Continued symptoms
Diazoxide 150 mg BID	Continued symptoms; fluid retention and tachycardia
Diazoxide 100 mg BID, HCTZ 25 mg daily	Continued symptoms
Prednisone 5 mg qAM, 2.5 mg in afternoon, diazoxide 100 mg BID, HCTZ 25 mg daily	Significant symptom relief
→ prednisone decreased at patient request	
Prednisone 5 mg qAM, diazoxide 100 mg BID, HCTZ 25 mg daily	Continued symptom relief
→ patient decreased own prednisone dose	
Prednisone 2.5 mg qAM, diazoxide 100 mg BID, HCTZ 25 mg daily	Moderate return of symptoms; she chose to continue this dose

TID, three times per day; BID, two times per day; qAM, every morning.

Patient 2

A 48-year-old woman presented at age 37 with episodes of mental fog and paresthesia when exercising or skipping meals. Her serum fasting glucose was 36 mg/dL. The 72-hour fast was stopped early when she developed neuroglycopenic symptoms. Blood glucose was 43–46 mg/dL, with insulin of 10.0 µIU/mL (2.6–24.6), proinsulin of 56.8 pmol/L (0–18.8), and C-peptide of 1.5 mg/mL (1.1–4.4). CT, MRI, and endoscopic ultrasound did not localize a mass. ¹⁸F-DOPA-PET showed increased uptake in the head of pancreas, concerning for insulinoma, and increased activity in the tail. Exploratory laparotomy with intraoperative ultrasound and palpation of the pancreas did not localize a mass. A second surgery, with 75% removal of the distal pancreas, including tail and body, did not resolve her symptoms. Calcium-stimulated arteriography demonstrated 10-fold increase in the pancreas head. She tried several different medication regimens (Table 1). Verapamil 80 mg TID (monotherapy), combination of verapamil 80 mg TID with diazoxide 50 mg TID, and octreotide 50 µg BID subcutaneously did not control her symptoms. Diazoxide 150 mg BID caused fluid retention and tachycardia; therefore, the dose was decreased to 100 mg BID and hydrochlorothiazide (HCTZ) was started, but symptoms persisted. She started prednisone, initially at 5 mg in the morning and 2.5 mg in the afternoon, continuing diazoxide and HCTZ. Her symptoms resolved and blood glucose normalized. She could exercise without symptoms, and blood glucose ranged from 60 to 80 mg/dL. By age 42, she self-decreased her prednisone dose to 2.5 mg daily while continuing diazoxide and HCTZ. She stopped checking her blood glucose and endorsed symptoms with increased activity, but believed they were manageable taking glucose tabs as needed.

At age 44, an MRI and nuclear medicine study in a clinical trial showed findings consistent with a 9-mm insulinoma in the pancreas head; however, exploratory surgery did not find a mass. Presently, she remains on prednisone 2.5 mg daily, diazoxide, and HCTZ. She adheres to a strict vegan diet, with frequent meals, endorsing only rare hypoglycemic symptoms. Surveillance anatomic/functional imaging studies remain stable with no identified lesion (Fig. 2).

Fig. 2. Dotatate PET scan showed no identified lesion (Patient 2).

Discussion

Diazoxide is considered first-line medical therapy for symptom control, inhibiting release of insulin from β -cells by activating potassium channels [1–4]. With Patient 1, long-acting octreotide was used first-line with great efficacy. Somatostatin analogs preferentially bind somatostatin receptors (SSTR) on insulinomas, suppressing insulin secretion [1, 5]. Their efficacy may depend on SSTR subtype expression on the specific insulinoma [4]. They are considered second-line medical therapy for benign insulinomas; however, due to antiproliferative and antitumoral activity, they can be used first-line for malignant insulinomas [1, 4, 6]. Use of everolimus was considered during her recurrence, but was deferred, since her symptoms were controlled on octreotide and follow-up imaging was stable. Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), a kinase that stimulates cell growth, proliferation, and angiogenesis [7]. It was approved by the FDA in 2011 for treatment of non-operable and metastatic pNETs [1]. Long-term data is limited, but one report describes its successful use for 45 months [8]. It has been used in conjunction with long-acting octreotide [9].

For Patient 2, the use of diazoxide caused side effects. Roughly half of patients experience side effects, including fluid retention, hirsutism, gastrointestinal symptoms, rash, and palpitations [1, 4]. Her fluid retention necessitated use of HCTZ. She developed hirsutism on her knuckles, jawline, and upper lip, requiring laser hair removal. Notably, she had 75% of her distal pancreas removed, although a mass was not localized. Blind distal pancreatectomy is no longer recommended for non-localized insulinomas, due to high failure rates and morbidity [10, 11]. Prednisone was started after verapamil, octreotide, and diazoxide were ineffective. Diazoxide and octreotide can be used together, which was not tried. The optimal medical therapy after those two are unsuccessful is not clear. Calcium channel blockers, β -blockers, and phenytoin were used more commonly in the past. Due to unclear benefit and significant adverse effects, they are generally not recommended [1, 2]. Glucocorticoids control hypoglycemia by increasing insulin resistance, increasing gluconeogenesis, decreasing insulin synthesis, and decreasing uptake of glucose [1]. Prednisone is routinely used to treat ferrets with insulinomas. Doses of 2.5 mg daily can significantly improve human symptoms [12]. She has now been on prednisone for 10 years. Even long-term doses of 2.5 mg daily are associated with side effects and physiologic changes [13]. When prednisone was started, everolimus was not yet available. Everolimus can be effective in patients with a small tumor burden. It improves hypoglycemia in patients, even when there is no measurable antitumor effect [1].

Table 2. Medical therapies for treatment of unresectable insulinoma

Medication	Mechanism	Side effects	Dose	Comments
Diazoxide	Inhibits insulin release from pancreatic β -cells by opening potassium channels; increases hepatic glucose production; inhibits hepatic glucose uptake	Fluid retention, hirsutism, weight gain, GI symptoms, headache, rash, palpitations, renal dysfunction	3–8 mg/kg/day in 2 or 3 doses; increase until desired effects	Considered first-line; 50% of patients have side effects; can be used with somatostatin analog
Somatostatin analogs: octreotide, lanreotide	Interaction with SSTR has antiproliferative and antitumoral effects and regulates insulin secretion in pancreatic cells; highest affinity for SSTR ₂ , some affinity for SSTR ₅	Short-term: GI symptoms; long-term: gall stones or sludge	Oct: 20–30 mg IM q 4 weeks; Lan: 60–120 mg SC q 4 weeks; can start with short-acting form to test response	Considered second-line; can be used first-line for malignant insulinomas; most effective in insulinomas with high SSTR ₂ expression
Oral corticosteroid: prednisone, dexamethasone	Increases insulin resistance and gluconeogenesis; decreases insulin synthesis and glucose uptake	Skin thinning, ecchymosis, cushingoid appearance, acne, insomnia, altered mood, osteoporosis, cataracts, fluid retention, hypertension	Lowest dose that controls symptoms	Can be considered if diazoxide and SA not effective; dose as low as 2.5 mg daily can be effective
Everolimus	Inhibits mTOR, a protein kinase that regulates cell survival, growth, and angiogenesis; mTOR inhibition also induces peripheral insulin resistance and reduces proinsulin secretion by insulinoma cells	Rash, stomatitis, fatigue, hyperglycemia, nausea, opportunistic infections, interstitial lung disease, anemia	10 mg p.o. daily; 5 mg daily if full dose not well tolerated	Approved for treatment of non-operable and metastatic pNETs; Improved glycemic control in absence of antitumor effect; potential severe toxicity, limited long-term data
Novel somatostatin analog: pasireotide	Interaction with SSTR produces antiproliferative and antitumoral effects and regulates insulin secretion in pancreatic cells; high affinity for SSTR ₁ , SSTR ₂ , SSTR ₃ , SSTR ₅	Peripheral edema, headache, alopecia, GI symptoms, hyperglycemia	20–60 mg IM q 4 weeks	Not approved for treatment of pNETs, efficacy documented in case reports; more effective than SA for insulinomas with high SSTR ₅ expression
Sunitinib	Tyrosine kinase inhibitor; inhibits angiogenesis resulting in antitumor activity	Mucositis, rash, hand-foot syndrome, GI symptoms, fatigue, hypertension, neutropenia	37.5 mg p.o. qd	Approved for treatment of advanced pNETs; very limited data with insulinomas, may worsen hypoglycemia
Peptide receptor radionuclide therapy with ¹⁷⁷ Lu	Radioablation	Bone marrow suppression, renal toxicity	4.8–7.4 GBq per cycle	Number of cycles may vary; improves hypoglycemic symptoms and quality of life; limited availability

GI, gastrointestinal; SA, somatostatin analog; SSTR, somatostatin receptors; IM, intramuscular; SC, subcutaneous; mTOR, mammalian target of rapamycin; pNET, pancreatic neuroendocrine tumor. See [1, 4].

mTOR inhibition induces peripheral insulin resistance and reduces proinsulin secretion by insulinomas [4]. Side effects include stomatitis, rash, diarrhea, fatigue, opportunistic infections, anemia, and interstitial lung disease [4, 7]. While everolimus could be effective in Patient 2, the potential morbidity and mortality associated with its side effects may make continuing low-dose prednisone a better choice. Other new medical therapies are pasireotide (a novel somatostatin analog) and sunitinib (a tyrosine kinase inhibitor); however, they require further investigation (Table 2) [4].

Patients 1 and 2 have been successfully managed with medical therapy for 15 and 11 years, respectively. A widely cited Mayo Clinic series followed 237 insulinoma patients from 1927 through 1986, including 13 metastatic patients. Ten-year postoperative survival was 88% in patients with benign insulinomas versus 29% in metastatic insulinomas [14]. Another large study reviewed data between 1985 and 1994 from 30 European registries and reported 5-year survival of 55.6% in 81 metastatic patients [15]. This older data indicates long-term survival with unresectable insulinoma is unlikely; however, it does not incorporate the use of newer medications or advancements in medical technology, like continuous glucose monitors. Newer survival data is not readily available, due to the rarity of metastatic insulinomas, but it is reasonable that modern patients will have better survival rates.

Conclusion

While prednisone is not standard therapy, its synergistic effects can control symptoms in patients with unresectable insulinoma. Clinicians should be aware of available and emerging medical options. Patients with unresectable insulinomas will likely have better long-term survival rates than those quoted in historical literature. Additional studies are needed to elucidate these survival rates and the long-term efficacy of modern medical therapies.

Statement of Ethics

This manuscript has been cleared by the institutional review board. The patients have given written informed consent to publish the case (including publication images).

Conflict of Interest Statement

The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or U.S. Government. The authors have no multiplicity of interest to disclose.

Funding Sources

None.

Author Contributions

All individuals who qualify as authors have been listed; each has participated in the conception and design of this work, the analysis of data, the writing of the document, and the approval of the submission of this version. Dr. Spiro wrote the draft. Dr. Hoang and Dr. Shakir reviewed and critically edited the paper.

References

- 1 Matej A, Bujwid H, Wroński J. Glycemic control in patients with insulinoma. *Hormones (Athens)*. 2016 Oct; 15(4):489–99.
- 2 Taye A, Libutti S. Diagnosis and management of insulinoma: current best practice and ongoing developments. *Res Rep Endocr Disord*. 2015;5:125–33.
- 3 Baudin E, Caron P, Lombard-Bohas C, Tabarin A, Mitry E, Reznick Y, et al. Malignant insulinoma: recommendations for characterisation and treatment. *Ann Endocrinol (Paris)*. 2013 Dec;74(5–6):523–33.
- 4 Brown E, Watkin D, Evans J, Yip V, Cuthbertson DJ. Multidisciplinary management of refractory insulinomas. *Clin Endocrinol (Oxf)*. 2018 May;88(5):615–24.
- 5 Arnold R, Wied M, Behr TH. Somatostatin analogues in the treatment of endocrine tumors of the gastrointestinal tract. *Expert Opin Pharmacother*. 2002 Jun;3(6):643–56.
- 6 Okabayashi T, Shima Y, Sumiyoshi T, Kozuki A, Ito S, Ogawa Y, et al. Diagnosis and management of insulinoma. *World J Gastroenterol*. 2013 Feb 14; 19(6): 829–37.
- 7 Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011 Feb 10;364(6):514–23.
- 8 Thomas NJ, Brooke AM, Besser GM. Long-term maintenance of normoglycaemia using everolimus in a patient with disseminated insulinoma and severe hypoglycaemia. *Clin Endocrinol (Oxf)*. 2013 May;78(5):799–800.
- 9 Akahori H. Clinical remission of an inoperable malignant insulinoma by the combination treatment with octreotide and everolimus. *J Gen Fam Med*. 2019 Jan 11;20(3):107–10.
- 10 Hirshberg B, Libutti SK, Alexander HR, Bartlett DL, Cochran C, Livi A, et al. Blind distal pancreatectomy for occult insulinoma, an inadvisable procedure. *J Am Coll Surg*. 2002 Jun;194(6):761–4.
- 11 Goh BK, Ooi LL, Cheow PC, Tan YM, Ong HS, Chung YF, et al. Accurate preoperative localization of insulinomas avoids the need for blind resection and reoperation: analysis of a single institution experience with 17 surgically treated tumors over 19 years. *J Gastrointest Surg*. 2009 Jun;13(6):1071–7.
- 12 Novotny J, Janku F, Mares P, Petruzella L. Symptomatic control of hypoglycaemia with prednisone in refractory metastatic pancreatic insulinoma. *Support Care Cancer*. 2005 Sep;13(9):760–2.
- 13 Saag KG. Low-dose corticosteroid therapy in rheumatoid arthritis: balancing the evidence. *Am J Med*. 1997 Dec 29;103(6A):31S–9S.
- 14 Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma – incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clin Proc*. 1991 Jul;66(7):711–9.
- 15 Lepage C, Ciccolallo L, De Angelis R, Bouvier AM, Faivre J, Gatta G, et al. European disparities in malignant digestive endocrine tumours survival. *Int J Cancer*. 2010 Jun 15;126(12):2928–34.