Successful Long-Term Medical Management of Unresectable Insulinomas

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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.
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.
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).

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.
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].

Fig. 2. Dotatate PET scan showed no identified lesion (Patient 2).
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    | Fluid retention, hirsutism, weight gain, GI      | 3–8 mg/kg/day in 2 or 3 doses; increase  | Considered first-line; 50% of patients have side                           |
|                                   | channels; increases hepatic glucose production; inhibits hepatic glucose   | symptoms, headache, rash, palpitations, renal    | until desired effects                     | effects; can be used with somatostatin analog                             |
|                                   | uptake                                                                     | dysfunction                                       |                                           |                                                                          |
| Somatostatin analogs: octreotide, | Interaction with SSTR has antiproliferative and antitumoral effects and  | Short-term: GI symptoms;                         | Oct: 20–30 mg IM q 4 weeks; Lan: 60–120 | Considered second-line; can be used first-line for malignant insulinomas;|
| lanreotide                        | regulates insulin secretion in pancreatic cells; highest                   | long-term: gall stones or sludge                  | mg SC q 4 weeks; can start with          | most effective in insulinomas with high SSTR2 expression                  |
|                                   | affinity for SSTR2, some affinity for SSTR5                                |                                                  | short-acting form to test response       |                                                                          |
| Oral corticosteroid: prednisone,  | Increases insulin resistance and gluconeogenesis; decreases insulin       | Skin thinning, ecchymosis, cushingoid appearance,|                                           |                                                                          |
| dexamethasone                      | synthesis and glucose uptake                                              | acne, insomnia, altered mood, osteoporosis,      |                                           |                                                                          |
|                                   |                                                                          | cataracts, fluid retention, hypertension         |                                           |                                                                          |
| Everolimus                         | Inhibits mTOR, a protein kinase that regulates cell survival, growth,    | Rash, stomatitis, fatigue, hyperglycemia, nausea,| 10 mg p.o. daily; 5 mg daily if full   | Approved for treatment of non-operable and metastatic pNETs; improved   |
|                                   | and angiogenesis; mTOR inhibition also induces peripheral insulin        | opportunistic infections, interstitial lung       | dose not well tolerated                  | glycemic control in absence of antitumor effect; potential severe       |
|                                   | resistance and reduces proinsulin secretion by insulinoma cells           | disease, anemia                                  |                                           | toxicity, limited long-term data                                         |
| Novel somatostatin analog:         | Interaction with SSTR produces antiproliferative and antitumoral effects | Peripheral edema, headache, alopecia, GI         | 20–60 mg IM q 4 weeks                    |                                                                          |
| pasireotide                        | and regulates insulin secretion in pancreatic cells; high affinity for    | symptoms, hyperglycemia                          |                                           |                                                                          |
|                                   | SSTR1, SSTR2, SSTR3, SSTR5                                               |                                                  |                                           |                                                                          |
| Sunitinib                          | Tyrosine kinase inhibitor; inhibits angiogenesis resulting in antitumor  | Mucositis, rash, hand-foot syndrome, GI symptoms, | 37.5 mg p.o. qd                      | Approved for treatment of advanced pNETs; very limited data with        |
|                                   | activity                                                                  | fatigue, hypertension, neutropenia               |                                           | insulinomas, may worsen hypoglycemia                                     |
| Peptide receptor radionuclide      | Radioablation                                                              | Bone marrow suppression, renal toxicity          | 4.8–7.4 GBq per cycle                    | Number of cycles may vary; improves hypoglycemic symptoms and quality of|
| therapy with ¹⁷⁷Lu                  |                                                                          |                                                  |                                           | 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.

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