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CASE REPORT

Pasireotide use for the treatment of endogenous hyperinsulinemic hypoglycemia refractory to conventional medical therapy: A case report and review of the literature

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Abstract

Insulinomas are rare neuroendocrine pancreatic tumors that can be associated with severe episodes of hypoglycemia, leading to significant morbidity and mortality. These tumors are often difficult to localize, and hypoglycemia control can be challenging since glucose levels can be resistant to conventional therapies. Pasireotide is a novel somatostatin analog with a high affinity to multiple somatostatin receptors. It has up to 40 times higher affinity for somatostatin receptor subtype 5 in comparison with octreotide, leading to a higher inhibition of insulin release from beta cells. There are few case reports regarding the use of pasireotide in refractory hyperinsulinemic hypoglycemia. We describe a challenging case of endogenous hyperinsulinemic hypoglycemia refractory to standard medical treatment, in which pasireotide was used. In this case, imaging studies and calcium stimulation testing failed to localize an insulin-secreting tumor in an 83-year-old woman. Glucose levels remained low despite treatment with diazoxide, verapamil, and octreotide, necessitating the use of IV dextrose solutions. After starting subcutaneous (SC) pasireotide 0.9 mg twice a day, there was a significant improvement in the frequency and severity of hypoglycemic events, allowing the patient to be discharged from the hospital without needing IV glucose support.

KEYWORDS

insulinoma, neuroendocrine tumor, pasireotide, refractory hypoglycemia

1 | INTRODUCTION

Insulinomas are neuroendocrine tumors characterized by an overproduction of insulin, leading to episodes of hypoglycemia. They are mostly sporadic but can also occur as part of an inherited syndrome such as multiple endocrine neoplasia syndrome type 1 (MEN-1). The incidence of insulinomas is estimated to be 1–4 cases/million/year.[1] The typical clinical presentation is fasting hypoglycemia, but cases having exclusive postprandial episodes have also been reported.[2]

The diagnosis of insulinomas is made by establishing inappropriately high insulin levels during episodes of hypoglycemia with a negative drug screen for insulin

secretogogues. Localization of these tumors can be challenging as it is not always possible to identify them in imaging studies. Surgical resection of the tumor is the treatment of choice.[3] However, the tumor is not always resectable, and some patients refuse surgery or are not candidates for surgical intervention. Medical therapy is commonly necessary for such patients. Therapeutic options include diazoxide, verapamil, and the somatostatin analog octreotide.[4] Some tumors are refractory to these interventions, and controlling hypoglycemia without intravenous glucose becomes difficult.

Pasireotide is a novel somatostatin analog that has a high affinity for multiple somatostatin receptors (SSTR). It has up to 40 times higher affinity for SSTR 5 than octreotide, leading to more potent inhibition of insulin release from beta cells.[4] There are few case reports of its use in insulinomas refractory to standard medical therapy.[1,3,5]

We report a case of endogenous hyperinsulinemic hypoglycemia refractory to guideline-recommended medical therapy, in whom pasireotide resulted in more effective control of hypoglycemia.

2 | CASE DESCRIPTION

An 83-year-old woman with a history of hypothyroidism, chronic obstructive pulmonary disease (COPD), and stage 1 gastric adenocarcinoma status postresection was admitted to the hospital with recurrent loss of consciousness associated with hypoglycemia.

She first presented 8 years before our evaluation with frequent early morning nausea, shakiness, and diaphoresis that improved after eating. These episodes were becoming more frequent, and they were sometimes associated with loss of consciousness. Biochemical testing when she was symptomatic revealed a blood glucose (BG) level of 45 mg/dl within appropriately normal levels of C-peptide (1.9 ng/ml), insulin (6.9 uIU/ml), and proinsulin (13.3 pmol/L). Her anti-insulin antibodies and hypoglycemia panel were negative. Further workup ruled out adrenal insufficiency. Her TSH was within normal limits on levothyroxine 50 mcg daily. On another occasion, she was found to have a BG of 35 mg/dl with a C-peptide of 1.7 ng/ml and an insulin level of 4 uIU/ml. She was diagnosed with endogenous hyperinsulinism and was prescribed diazoxide 100 mg 3 times daily with subsequent resolution of the hypoglycemia. She underwent magnetic resonance cholangiopancreatography (MRCP), revealing a 2 mm T2 hyperintense focus within the pancreatic head, suggestive of a small cyst.

Several years later, she experienced recurrent falls with fasting hypoglycemia in the range of 30–50 mg/dl on a nearly daily basis. She underwent pancreatic protocol CT imaging that did not reveal a definitive pancreatic mass but did show a 9 mm subtly enhancing area in the pancreatic head. Endoscopic ultrasound (EUS) showed irregularity in the head of the pancreas, and a biopsy showed no evidence of tumor. Her diazoxide dose was increased to 125 mg three times daily which helped prevent further episodes of loss of consciousness. However, fasting BG levels continued to run low in the range of 50–70 mg/dl. She underwent a selective arterial calcium stimulation (SACS) with venous sampling to localize a possible insulinoma (Figure 1). There was a borderline increase in insulin levels during calcium stimulation of the superior mesenteric artery, corresponding to the uncinate process, but this did not correlate with the 9 mm lesion previously identified in the head of the pancreas. Additionally, the rise in insulin did not meet the criteria for localization of an insulinoma (i.e., a twofold increase in insulin levels following stimulation).

As her SACS failed to localize an insulinoma, and because of the high surgical risk based on her age and COPD, it was decided to avoid partial pancreatectomy as a therapeutic option and to aim for optimization of medical therapy. Over the following year, her fasting BG readings remained in the range of 35–40 mg/dl, and she started to report early morning confusion and more frequent falls. She was advised to take two tablespoons [15 g of carbohydrates] of uncooked cornstarch at bedtime that was later increased to 4 times a day. This normalized glucose levels for several months, but the hypoglycemia recurred. She was started on verapamil 80 mg daily, which could not be further increased because of symptomatic bradycardia. She reported more frequent syncopal episodes. Over time, she developed hypoglycemia unawareness, frequently fainting without prodromal symptoms. Octreotide 150 mcg three times daily was added and was then switched to Octreotide LAR 30 mg once monthly intramuscular injections.

Despite being on diazoxide, verapamil, and octreotide LAR, she suffered hypoglycemia-associated fall at home that caused an orbital fracture. She was admitted to the hospital and started on dextrose 10% infusion due to persistently low BG readings. DOTATATE PET/CT did not show any evidence of an avid neuroendocrine tumor. Repeat EUS revealed multiple subcentimeter cysts in the head and body of the pancreas. These were felt to be intraductal papillary mucinous neoplasms (IPMNs). She was evaluated by the general surgery service for possible total pancreatectomy, but she was not considered a good surgical candidate because of her comorbidities. Attempts were made to wean the IV dextrose infusion off, but she had recurrent hypoglycemia despite

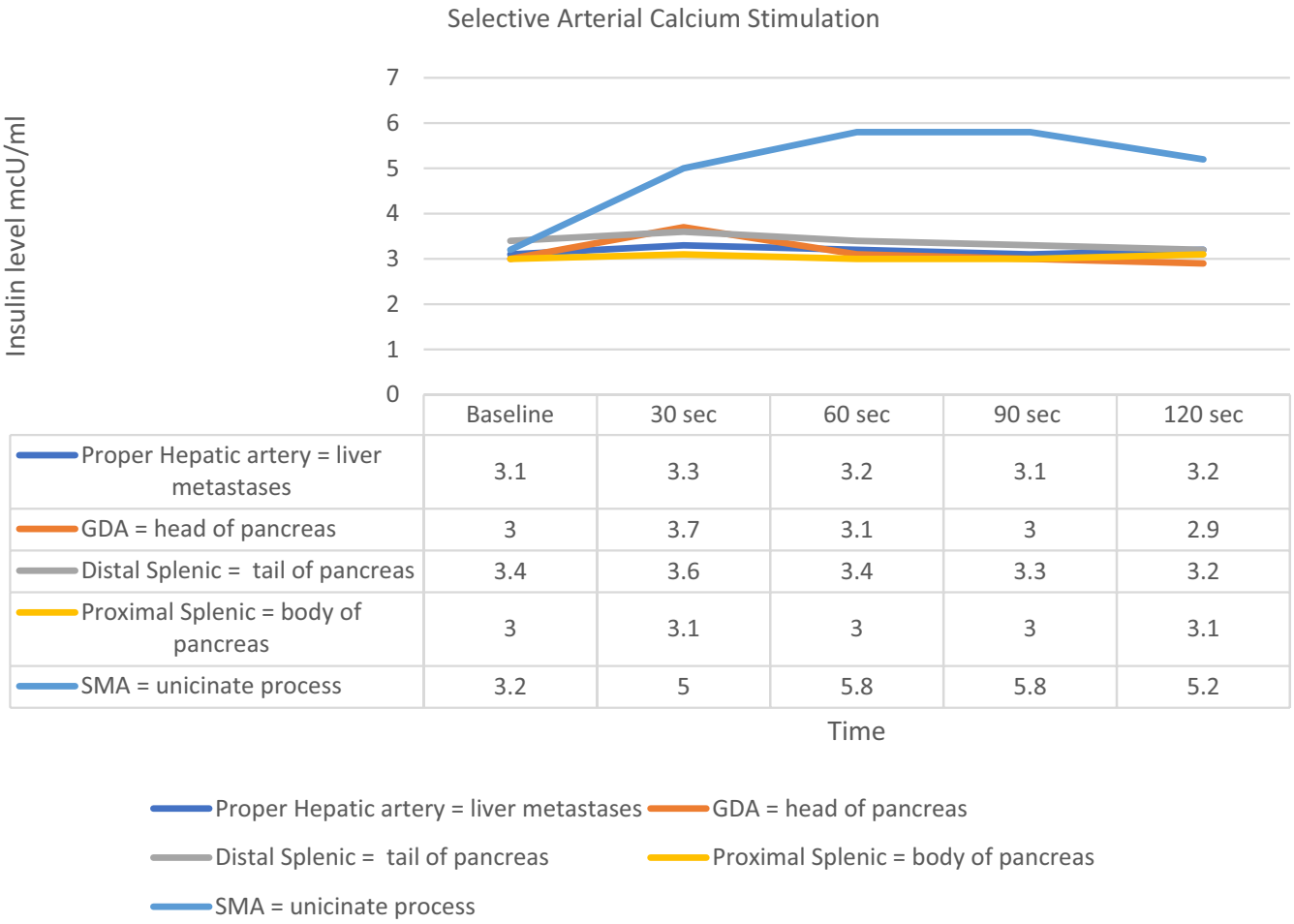

FIGURE 1 Selective arterial calcium stimulation [SACS]: Under conscious sedation, 5Fr catheters were inserted into both the right femoral artery and vein. Under fluoroscopic guidance, the venous catheter was positioned in the right hepatic vein for blood sampling. After selective catheterization, a calcium gluconate bolus was rapidly injected into the proper hepatic, gastroduodenal [GDA], splenic, and superior mesenteric [SMA] arteries. Blood was obtained from the right hepatic vein before the injection (baseline, t = 0) and 30, 60, 90, and 120 s after calcium injection. Five minutes were allowed between arterial stimulations. Insulin concentrations of these blood samples were determined, and a positive response to the injection of calcium was defined as at least a doubling of the insulin level at more than one time point after the injection

changing octreotide to the immediate-release formulation and titrating the dose to 500 mcg three times a day (Figure 2). Due to the continued requirement for IV glucose solution, octreotide was changed to pasireotide 0.9 mg subcutaneously every 12 h. Within 24 h of the first pasireotide injection, her serum glucose levels started to improve, and the D10 was gradually weaned off. Glucose levels ranged between 68 and 395 mg/dl for the remainder of her hospitalization, with no recurrence of hypoglycemia.

She was discharged to a nursing home for further care on pasireotide 0.9 mg subcutaneously twice a day and diazoxide 125 mg three times daily. Because of lack of insurance coverage for pasireotide, she could not continue this therapy and suffered another hypoglycemia-associated fall complicated by a hip fracture.

3 | DISCUSSION

In this report, we describe a case of hyperinsulinemic hypoglycemia refractory to conventional medical therapy. The initiation of pasireotide allowed the patient to be discharged without the need for dextrose-containing IV fluids.

Localization studies failed to show an obvious tumor despite documentation of endogenous hyperinsulinemic hypoglycemia. The patient continued to have recurrent symptomatic hypoglycemia despite the standard of care therapy.[4] The hypoglycemia was successfully treated with pasireotide, and the patient was discharged to a nursing home off IV glucose solutions.

Somatostatin is a pancreatic hormone with regulatory effects on insulin and glucagon secretion. It also plays a

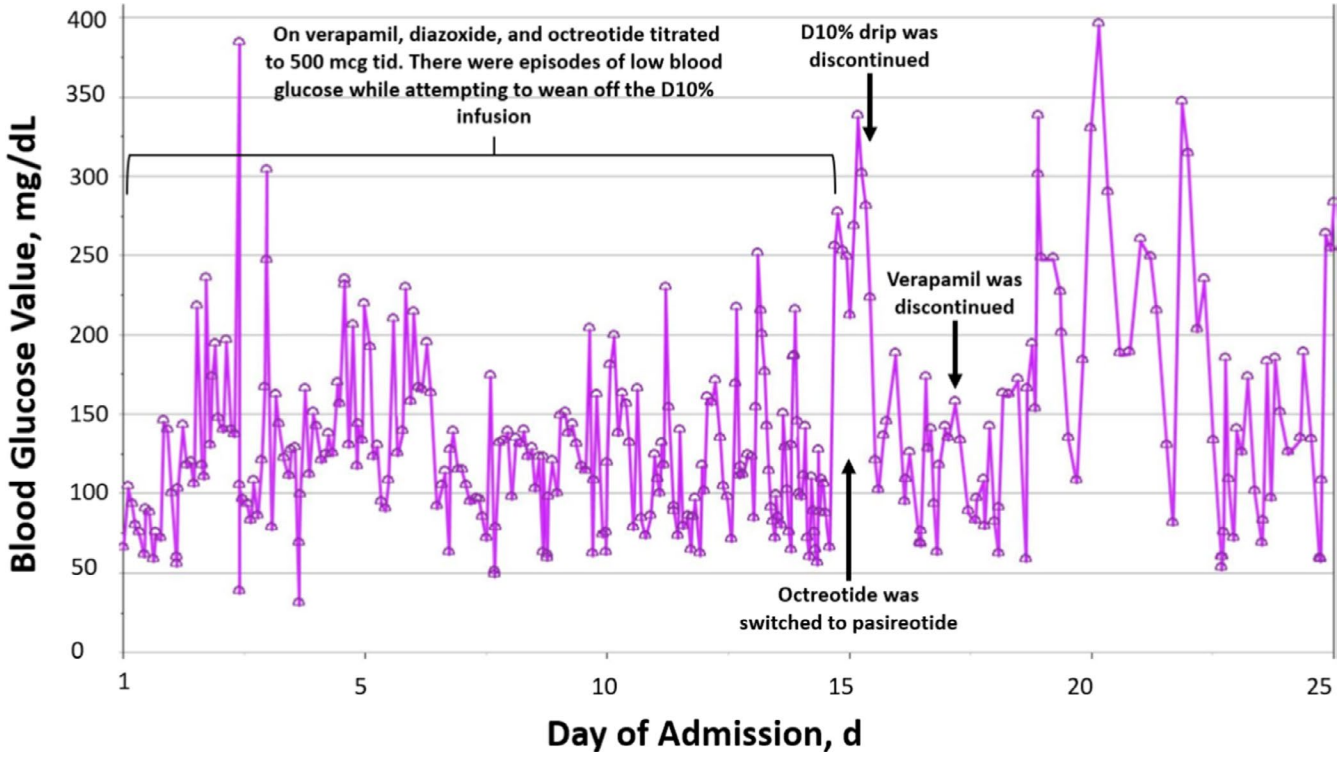

FIGURE 2 Glucose tracing during hospital admission. Some of the hyperglycemia readings resulted from overcorrecting the episodes of hypoglycemia with IV dextrose

role in regulating cell proliferation through interaction with five somatostatin receptors (SSTR 1–5). These receptors have distinct structures, functions, and tissue distribution.[4] Previous studies have shown that SSTR2 and 5 are potent inhibitors of insulin release from pancreatic islet cells.[6,7] In some pancreatic neuroendocrine tumors, SSTR1 and 2 are present in all cases,[8] while in other cases, SSTR2 and 5 are the main subtypes present in insulinomas.[9]

Endogenous somatostatin has a high affinity to all SSTRs, while somatostatin analogs have different affinities for different SSTRs.[5] Octreotide and lanreotide are two somatostatin analogs used to treat gastroenteropancreatic neuroendocrine tumors. They inhibit the release of hormones by the tumor, and they also have an antiproliferative effect. Both have a higher affinity to SSTR2 and much less affinity to SSTR5. On the contrary, pasireotide is a second-generation somatostatin analog that binds SSTRs more broadly. It can bind to SSTR 1,2,3, and 5, and has up to 40 times higher affinity for SSTR 1 and 5 compared with octreotide.[4] One of the proposed explanations for the successful use of pasireotide in some cases of insulinoma is a low expression of SSTR2 and high expression of SSTR5 in these tumors.[4] Unlike pasireotide, conventional somatostatin analogs have a weak affinity for SSTR5.

Pasireotide is currently FDA approved for the treatment of acromegaly and Cushing disease. Hyperglycemia is one of the most common side effects of pasireotide use, occurring in 57% of cases.[10] The hyperglycemic effect of pasireotide occurs due to decreased insulin, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide secretion.[11]

There are only a few case reports regarding the use of pasireotide in treating insulinomas refractory to conventional therapies. Tirsosh et al. described a case of metastatic insulinoma in which pasireotide resulted in better hypoglycemia control than lanreotide or everolimus.[5] In their reported case, pasireotide was switched to everolimus due to disease progression. However, this worsened hypoglycemia events, and everolimus was switched back to pasireotide with improved hypoglycemia control. Siddiqui et al. reported 3 cases of tumor-induced hypoglycemia refractory to conventional medical therapy. Pasireotide was successfully used in all 3 cases with subsequent improvement of hypoglycemia.[3] In two of their patients, the hypoglycemia resolved completely.

Data on the antiproliferative effect of pasireotide are limited. In one study, patients with carcinoid tumors of the digestive tract were randomly assigned to receive either pasireotide LAR or octreotide LAR. The primary and secondary outcomes of the study were symptomatic control and tumor response, respectively. There was a non-statistically significant improvement in tumor control rate at 6 months in patients treated with pasireotide

LAR compared to octreotide LAR (62.7% vs. 46.2%). Additionally, pasireotide LAR was associated with a more prolonged progression-free survival compared with octreotide LAR.[11]

Pasireotide successfully improved the hypoglycemia in our patient, but the continuation of therapy was not possible due to lack of insurance coverage for a non-FDA-approved indication. There is an ongoing effort to obtain approval for her to start back on pasireotide.

4 | CONCLUSION

Pasireotide should be considered for patients with endogenous hyperinsulinemic hypoglycemia refractory to conventional therapy. In our case, the patient was discharged to a nursing home without needing an IV dextrose solution. Further studies regarding the use of pasireotide in patients with refractory hypoglycemia are needed.

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CONFLICTS OF INTEREST
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AUTHOR CONTRIBUTION
Hasan Husni reviewed the literature and prepared the manuscript. Sara A Khan prepared the case description and figures. Buraq Alghaieb reviewed and summarized the literature. Mohammed S. Abusamaan prepared figures and revised the manuscript. Thomas W. Donner involved in the final revision of the manuscript. Amir H. Hamrahian supervised the preparation of the manuscript.

CONSENT
A written consent to publish this case has been obtained from the patient.

DATA AVAILABILITY STATEMENT
Data sharing not applicable – no new data generated, or the article describes entirely theoretical research.

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