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CASE REPORT

Recurrence of Metastatic Pro-insulinoma Nearly 50 Years After Subtotal Pancreatectomy

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Background

The incidence of functional pancreatic neuroendocrine tumors (PNET) is reported at approximately four cases per one million persons [1]. Patients with insulin-producing PNETs classically present with Whipple's triad consisting of hypoglycemic symptoms after fasting (neuroglycopenia and sympathetic stimulation), hypoglycemia at the time of the symptoms, and symptom relief with treatment of hypoglycemia or ingestion of food [2]. Pro-insulinomas are an exceedingly rare subtype of PNET producing the precursor form of insulin, of which only a handful has been reported in the literature [3–7]. They may present in identical clinical fashion, as proinsulin has approximately 10% of the biological activity as mature insulin [8]. The diagnosis requires high clinical suspicion as standard testing for hypoglycemia (fasting serum glucose, insulin, and C-peptide) may miss hyperproinsulinemia, which presents with low or normal insulin levels [8]. Oral glucose tolerance test may aid in differentiating reactive hypoglycemia from an insulinoma and specific proinsulin level should be obtained. Although these tumors can metastasize, the course remains generally indolent, and recurrence has been reported as low as 3 to 16% [9–11]. Recent targeted therapeutic agents have opened the door for alternative treatment options in patients with advanced well-differentiated tumors, particularly those whose metastatic hormonally active tumors were unresectable [12–14].

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Case Presentation

We present the case of a patient with metastatic functional pro-insulinoma recurring nearly 50 years after initial diagnosis and surgical extirpation. Our patient is a 78-year-old retired male surgeon with severe hypoglycemia requiring infusion of dextrose 10% solution nightly. The patient underwent subtotal pancreatectomy and splenectomy for pro-insulinoma at age 29 when he was a medical student. In fact, the patient was included as a control subject in a case series of patients with factitious hypoglycemia published 40 years ago [3]. There was no family history of multiple endocrine neoplasia, and he did not manifest additional syndromic conditions. Despite later being diagnosed with metastatic NET at subsequent laparotomies of the lymph nodes and liver 1 and 6 years post subtotal pancreatectomy, respectively, he was reportedly asymptomatic since initial operation. He had not tolerated treatment with diazoxide or streptozocin and, with limited therapeutic options, he lived out his surgical career "with a candy bar in my pocket". After retirement, he underwent a surgical procedure for scoliosis and was noted to have severe hypoglycemia (fasting glucose 30-67 mg/dL) without symptoms as verified by inpatient nursing staff and his family. Biochemical analysis demonstrated recurrence of pro-insulinoma, yet multiple imaging modalities did not identify any definite metastatic foci.

Biochemical studies included proinsulin level 1769 pmol/L (ref. 3–20 pmol/L), insulin 70.7 uIU/mL (ref. 2–29 uIU/mL), C-Peptide 4.1 ng/mL (ref. <13 ng/mL), glucose 102 mg/dL (ref. 70–99 mg/dL), Chromogranin-A 385 ng/mL (ref. <93 ng/mL), LDH 549 U/L (ref. 313–618 U/L). CMP and

CBC were within normal range. Imaging demonstrated no definite metastatic foci. Octreotide nuclear medicine imaging demonstrated physiologic uptake only (Fig. 1). Computed tomography demonstrated sub-centimeter cystic liver lesions that could not be definitively classified (Fig. 2). Given his advanced age and comorbidities, inpatient fast and EUS of pancreas were not initially recommended. He was receiving nightly intravenous (IV) infusions of dextrose in order to avoid severe hypoglycemia and to minimize disruptions in his sleep for blood glucose checks.

The patient and family preferred nonsurgical approach if possible with goal of optimizing quality of life and wean off nightly IV dextrose infusions. To this end, everolimus therapy was initiated with the goal of stabilizing glucose levels and maintaining disease stability [12, 13, 15]. Three months later, the patient was able to stop IV infusions and replace with a 2 am high-calorie nutritional supplement. Biochemical studies demonstrated still elevated proinsulin (2030 pmol/L) and (insulin 92.1 uIU/mL), and magnetic resonance abdominal imaging with gadoxetate disodium identified a 0.6 × 1.6 area at the pancreatic bed that could potentially represent recurrent tumor. The patient was able to wean off the supplement and a ^{68}gallium-DOTATATE positron emission tomography study performed 9 months after initiation of everolimus therapy demonstrated no evidence of disease (Fig. 3).

Discussion and Review of the Literature

Patients with insulin-producing PNETs classically present with Whipple's triad consisting of hypoglycemic symptoms after fasting (neuroglycopenia and sympathetic stimulation), hypoglycemia at the time of the symptoms, and symptom relief with treatment of hypoglycemia (blood glucose approximately 40 mg/dL) or ingestion of food [2]. The incidence of functional PNET is reported at approximately four cases per one million persons, although recent reports suggest an increasing incidence in PNET [1, 16]. Functional PNETs are usually detected at an earlier age than nonfunctional tumors, presumably to the symptoms and manifestations of hormonal excess. Insulinomas can been associated with hereditary syndromes such as multiple endocrine neoplasia type 1, von Hippel-Lindau, neurofibromatosis type 1 (NF1), and tuberous sclerosis (TSC); however, there are no reports of pro-insulinoma in association with any of these syndromes [8].

Pro-insulinomas are an exceedingly rare subtype of PNET producing the precursor form of insulin. Proinsulin is produced in pancreatic β cells; it is cleaved in the trans-golgi network to form equimolar concentrations of insulin and C-peptide. Although pro-insulinomas do not secrete cleaved mature

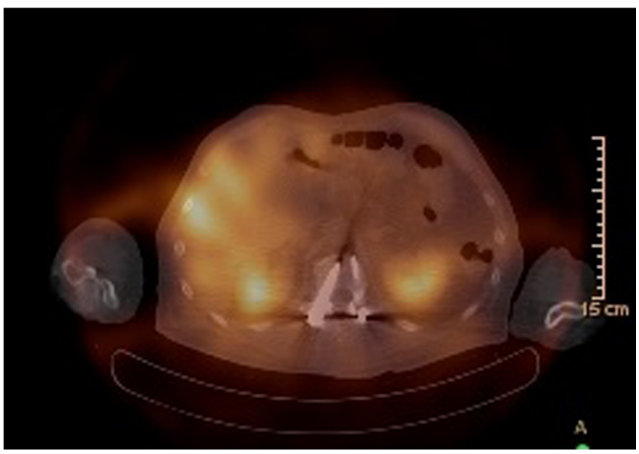

Fig. 1 Octreotide nuclear medicine imaging demonstrated physiologic uptake in a 78-year-old male patient with recurrent pro-insulinoma

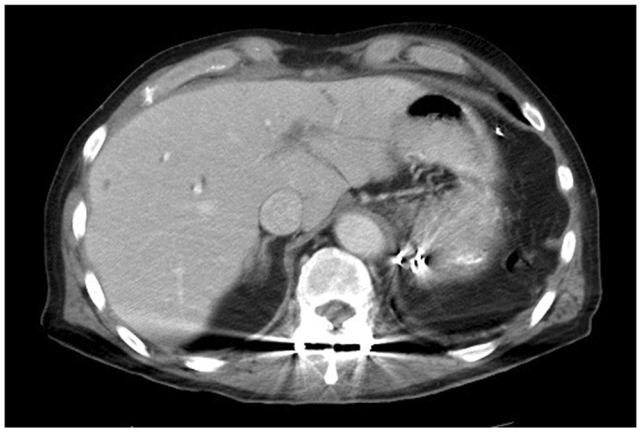

Fig. 2 Computed tomography demonstrated sub-centimeter cystic liver lesions that could not be definitively classified

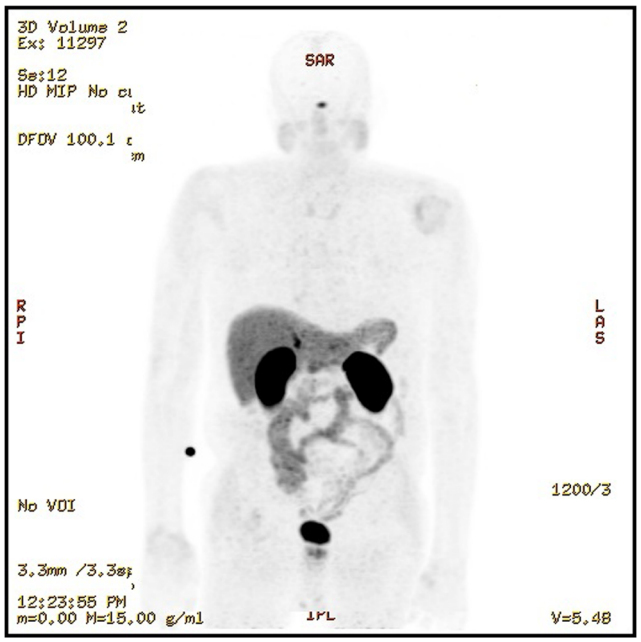

Fig. 3 ^{68}Ga-DOTATATE positron emission tomography in a patient with suspected recurrent insulinoma. There is physiologic uptake in the pituitary, kidneys, and adrenal glands

insulin, the precursor form can also activate insulin receptors. Thus, the clinical presentation is essentially identical. The diagnosis requires high clinical suspicion as standard testing for hypoglycemia may miss a pro-insulinoma. Insulin antibodies used in the original immunoassays to evaluate patients, including the one used at the time of our patient's initial diagnosis, were non-specific and reacted with both mature insulin and the uncleaved precursors allowing for diagnosis of both insulinoma and pro-insulinoma. Current immunoassays for insulin now utilize specific monoclonal antibodies which do not cross-react with precursor forms leading to normal or low levels of insulin in patients with pro-insulinomas [17]. Thus, requesting specific measurement of proinsulin levels may be helpful to avoid missed diagnosis. Cross-sectional imaging with 1–2 mm cuts is helpful in detecting these small, usually solitary lesions. Endoscopic, transgastric, or transduodenal ultrasound may be helpful in determining location of PNETs and endoscopic tattooing has been reported as a helpful adjunct for the surgeon [18]. Insulinomas may be distributed throughout the entire pancreas; as such enucleation—even if multiple lesions are present—is the preferred surgical strategy to maintain pancreatic function [16, 19]. The laparoscopic approach is considered standard of care for these indolent and usually benign neoplasms. More recently, endoscopic ethanol ablation has been introduced as an alternative treatment strategy for patients who are considered to be at significant high risk of morbidity and mortality for surgery [20].

Although insulinomas can metastasize, the course remains generally indolent. Studies evaluating long-term outcomes have reported recurrence as low as 3 to 16% [1, 9–11]. Therapy with somatostatin analogs has demonstrated improved progression-free survival in patients with metastatic well-differentiated PNETs [21]. Somatostatin analogs, which target somatostatin receptor 2 (sst2), may be less effective in treatment of insulinomas due to lack of expression of sst2. The newer agent pasireotide, which activates sstr 1, 2, 3, and 5, is under investigation as a potential therapy in PNETs [14, 22]. Recent targeted therapeutic agents have opened the door for treatment options in patients with advanced well-differentiated tumors. Advances in the understanding of the pathogenesis in PNETs has allowed for exploration of treatment with targeted therapeutic agents such as everolimus. In a randomized controlled trial, patients with well-differentiated advanced PNETs had a longer progression-free survival when treated with everolimus when compared to the placebo group [12, 13]. Common adverse events include stomatitis, diarrhea, rash, and hyperglycemia—a favorable side effect in the setting of hypoglycemia secondary to neuroendocrine tumor [12–16]. Everolimus is an inhibitor of the mammalian target of rapamycin (mTOR) pathway, a highly conserved protein kinase with roles in cell cycle control and proliferation. Dysregulation in mTOR pathway is present in TSC and NF1, and their associated increased risk of NETs prompted evaluation of mTOR inhibitors as potential therapeutic agents. In TSC, the mutated complex is upstream of mTOR in the PI3K/AKT/mTOR pathway and NF1 deficient cells show constitutive activation of mTOR. Furthermore, activation of mTOR has been shown to be a driver of insulinoma tumorigenesis, and insulinoma tumor specimens show higher levels of phosphorylated mTOR than normal pancreatic islet controls [23]. It is possible that pro-insulinomas are driven by similar cellular aberrations, although this may be difficult to confirm given the rarity of the tumor type and lack of pre-clinical models.

We report a fascinating case of a patient with documented recurrence of pro-insulinoma nearly 50 years following initial diagnosis and surgical resection. This is the longest described recurrence of pancreatic neuroendocrine tumor and particularly unique in the setting of a patient with pro-insulinoma.

Compliance with ethical standards Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflict of interest James Yao is a consultant for Novartis, Ipsen. The remaining authors declare that they have no conflict of interest.

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