A case of metastatic insulinoma: Management and review of literature

Abstract

Insulin-secreting tumors are the most common hormones, producing neoplasms of the gastrointestinal tract. Among them, only 10% of insulinoma is malignant. We report a rare case of malignant insulinoma in a 58-year-old female who presented with recurrent episodes of hypoglycemia and symptoms of neuroglycopenia, such as recurrent generalized tonic-clonic seizures. Evaluation revealed low fasting and random blood sugars with high levels of serum C-peptide, proinsulin, and insulin. Radio-imaging revealed mass in the head of the pancreas and multiple lymph nodal and liver metastases. Her symptoms were refractory to medical therapy with somatostatin analogs and were requiring frequent parenteral dextrose boluses. She was then subjected to the resection of mass and liver metastasectomy, following which addition of everolimus to somatostatin analog dramatically abolished her symptoms. She is symptom-free for the last 11 months on somatostatin analog and everolimus.

Key words: Everolimus, Insulinoma, Sandostatin.

INTRODUCTION

Insulinoma is rare functional neuroendocrine tumor (NET) of the pancreas with the incidence of four per million persons each year.[1] Despite its rare incidence, they are the most common functional NET.[2] In 1927, Wilder reported the first case of insulin secreting tumor in a patient who was a surgeon with 18 months of history of hypoglycemia; exploratory laparotomy revealed unresectable metastatic insulinoma.[3,4] However, it was not until 1929 that Roscoe Graham performed the first surgical resection of an insulinoma, relieving symptoms of hypoglycemia.[3,5] In 1935, Whipple and Frantz published a manuscript summarizing the historic advances that defined insulinoma, along with their own observations. This paper represented the first published account of the diagnostic “Whipple’s Triad” as (1) symptoms of hypoglycemia provoked by fasting, (2) circulating glucose level <50 mg/dL at the time symptoms presented, and (3) the relief of symptoms with the administration of glucose.[6] We report a case of a woman with metastatic insulinoma who was managed with both surgical and medical therapies rendering her asymptomatic.

CASE REPORT

A 55-year-old nondiabetic female presented with a history of recurrent generalized tonic-clonic seizures (GTCS) and frequent spells of lightheadedness, diaphoresis, associated with lethargy and hunger of 2 weeks duration. Her fasting as well as random blood sugar at the time of
symptoms was found to be very low (<50 mg/dl), with raised c-peptide and proinsulin levels. Evaluation revealed a mass lesion measuring 26 mm × 29 mm in the head of pancreas with multiple hepatic spaces occupying lesions, largest measuring 22 mm × 30 mm, and enlarged abdominal and inguinal lymph nodes. Fine-needle aspiration cytology of pancreatic mass revealed islet cell tumor. Whole body positron emission tomography-computed tomography (CT) revealed fluorodeoxyglucose (FDG) avid pancreatic mass, multiple hepatic lesions, and FDG avid cervical, axillary, mesenteric, and inguinal lymphadenopathy, the largest measuring 18 mm × 18 mm with maximum standard uptake value of 4.6 [Figure 1].

Due to the extensive disease, the patient was deemed unresectable by surgeons and planned for medical management. The patient despite receiving multiple doses of octreotide remained symptomatic with hypoglycemic episodes and occasional GTCS, requiring dextrose boluses.

The patient was then discussed in the institutional tumor board and was taken up for cytoreductive surgery in view of refractory symptoms not responding to medical therapy. She underwent resection of pancreatic mass and hepatic metastasectomy. Histopathology confirmed it to be pancreatic insulinoma. Following surgery, the patient remained asymptomatic for a few days but had relapse of symptoms within 1 week although less severe than before and not associated with any GTCS. DOTANOC scan showed two hypodense somatostatin receptors expressing lesions in the liver, the largest measuring 23 mm × 33 mm [Figure 2].

She was then restarted on daily multiple doses of octreotide which was later substituted by long-acting analog Sandostatin LAR. Her symptoms markedly reduced over a span of 1 week although not completely asymptomatic with hypoglycemic episodes occurring infrequently (once in a day or two). Everolimus was started at a dose of 10 mg once daily to which she responded dramatically and became symptom-free over a span of next 2 weeks. At present, she is symptom-free for the last 10 months on Sandostatin LAR and everolimus. If she relapses with the symptoms in future, she can be subjected to peptide receptor radionuclide therapy (PRRT).

**DISCUSSION**

Pancreatic endocrine tumors are usually well differentiated, and they are classified as functional or nonfunctional based on their ability to secrete hormones. The majority of them are functional tumors, and insulinoma is the most common functional NET. Nonfunctional tumors comprise approximately 30% of pancreatic endocrine tumors, and the majority of these will have metastases at presentation. The majority of insulinoma are small, measuring <2 cm. Although the large majority of insulinoma are sporadic, up to 10% may be associated with hereditary multiple endocrine neoplasias Type 1 (MEN-1). Except insulinoma which is rarely diagnosed at an advanced age as well metastatic only in about 10% of the cases, most of the other pancreatic endocrine tumors are frequently diagnosed at a late stage, with approximately 65% of patients presenting with unresectable or metastatic disease. These patients have a poor prognosis with the median survival time of 24 months. We report a 58-year-old woman with a functional pancreatic NET (PNET), metastatic insulinoma.

Our patient presented with recurrent episodes of hypoglycemia manifesting as GTCS. She was diagnosed to have pancreatic mass and unresectable metastasis. Many therapeutic options have been used to treat hypoglycemia in insulinoma patients with unresectable metastases. Octreotide, used successfully in the treatment of insulinoma, has a short biological half-life of 100 min, requiring multiple daily doses, and response rates vary among the patients that can be correlated to the expression of a number of somatostatin receptor subtypes 2 and 5. Octreotide had multiple episodes of hypoglycemia manifesting as dizziness, diaphoresis, and palpitations, which required bolus dextrose and maintenance dextrose infusions. This can be explained with the extensively metastatic disease to liver and multiple regional and nonregional lymph nodes. Octreotide had many side effects including life-threatening arrhythmias and conduction defects in about 10% cases, with increased risk of these complications in patients with preexisting cardiac illness. Fortunately, our patient did not develop any such complications,
but caution is recommended when octreotide is administered to at-risk patients.\textsuperscript{[13]}

Due to the persistence of symptoms, our patient was subjected to cytoreductive surgery in the form of resection of pancreatic mass and hepatic metastasectomy. There is wide range of noninvasive as well as invasive methods of preoperative localization of PNETs. Noninvasive imaging modalities include abdominal ultrasonography, bolus-enhanced helical CT, magnetic resonance imaging, and somatostatin receptor scintigraphy. Invasive studies are selective angiography, transhepatic portal venous sampling, endoscopic ultrasonography (EUS), and selective arterial calcium stimulation (SACS). While preoperative localization increases intraoperative success, some have argued that preoperative localization is not necessary. Among noninvasive modalities, CT has an average sensitivity of 70%. EUS and SACS have better sensitivity in detecting smaller lesions, commonly encountered with MEN syndromes. Malignant or metastatic insulinoma, spreading primarily to lymph node or liver, is a rare condition accounting for only 5–12% of reported cases of insulinoma.\textsuperscript{[12]} These patients have a poor prognosis, with a median survival period of approximately 2 years. The initial surgery for tumor removal or diagnosis is the most important factor in the management of malignant insulinoma. Patients with a reasonable performance status, minimal extrahepatic disease, and resectable primary tumor are candidates for cytoreductive surgery. Despite cytoreduction, our patient had relapses of hypoglycemic episodes within 1 week of surgery.

Our patient was restarted on octreotide daily which was further substituted by long-acting analog Sandostatin LAR once 4 weekly. Her symptoms markedly reduced over a span of 2 weeks. The chemotherapeutic agents, everolimus and sunitinib, have been recently approved for the management of advanced insulinoma, with promising progression-free and overall survivals.\textsuperscript{[7,10]} Patients with PNETs who were randomized to therapy with a dose of 37.5 mg of sunitinib daily had a median progression-free survival of 11.4 months compared with 5.5 months with placebo.\textsuperscript{[13]} Given the positive response seen in these patients described in the literature, such patients should be considered for everolimus protocol for intractable hypoglycemia.

In summary, we present a rare case of metastatic insulinoma, who was managed with multidisciplinary approach including surgery and medical therapy. The patient is on regular follow-up and is symptom-free for the last 10 months. Relapse of symptoms is planned to be managed with PRRT.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES