Case Report

Progressive Malignant Insulinoma with Multiple Liver Metastases: A Case Report

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Abstract

Background: Insulin-secreting tumors are the most common hormone-producing neoplasm of the gastrointestinal tract. Only 10 percent of overall cases of insulinoma have malignant variants, which have a poor prognosis.

Cases Report: The present study reports an unusual case of pancreatic neuroendocrine tumor associated with hypoglycemia and liver metastasis as the initial presentation followed a rapidly progressive clinical course. A few cases of malignant insulinoma were reported with favorable responses in the literature. This research presents a patient with resistant malignant insulinoma who could not undergo an operation and received treatment with somatostatin analogs (S.S.A.), Peptide Receptor Radionuclide Therapy (PRRT), and other supportive care that was inappropriate.

Conclusion: Early diagnosis and extensive treatment are auspicious for improving the prognosis of malignant insulinoma, and proper treatment with medications would increase the quality of life of patients. Nevertheless, unfortunately, late patient referrals, socioeconomic conditions, and being infected with Covid-19 disease resulted in death.

Keywords: Metastasis, Malignant insulinoma, Hypoglycemia

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Introduction

A functional pancreatic neuroendocrine tumor (pNET), referred to as an insulinoma, develops from islet beta cells, which produce excessive insulin and lead to hypoglycemia. The most prevalent functional

pNET is insulinoma, which has a prevalence of one to four cases per million individuals[1]. Malignant insulinoma is uncommon, and only 10 percent of total insulinoma cases are diagnosed with this type of disease[2].

The only indicator of malignancy, according to the World Health Organization (WHO), is the existence of metastasis, and malignant insulinoma is observed to be correlated with a greater risk of recurrence and death[3].

Malignant insulinoma has a poor prognosis because of rapid cell proliferation. Surgical debulking or hepatic embolization can be used if metastasis is observed at the time of operation or in the imaging examinations, or if the patient cannot undergo an operation. An alternative option is drug therapy using diazoxide, octreotide L.A.R. (long-acting release), everolimus, or chemotherapy[4].

Because of the disease's scarcity, there are not many available records of patients with malignant insulinomas. Therefore, it is unknown what type of therapy is optimal and most influential in these patients. This research reports a metastatic insulinoma in a 41-year-old woman, presenting with rapidly progressive wasting associated with hypoglycemia.

Case Report

In October 2020, a 41-year-old woman without previous medical history presented with anxiety, dizziness, change of personality and behavior, and generalized intermittent abdominal pain and was admitted to the emergency department of Loghman Hakim Hospital, Tehran, Iran.

Also, she has often had epigastric pain, nausea and vomiting, chronic non-bloody and watery diarrhea, and unintentional weight loss of 10 kg for three months; on an outpatient basis, she underwent periodic treatment and did not consent to the diagnostic work of her disease. On physical examinations, she was in a state of confusion, with hepatomegaly and lower extremity edema.

At the first evaluation, initial laboratory tests suggested that the patient's symptoms, proposed for hypoglycemia and liver dysfunction and appropriate treatment, were performed with intravenous dextrose and other supportive care.

Following the history, she denied alcohol consumption or using antihyperglycemic agents and other drugs; she had no family history of endocrine tumors or diseases.

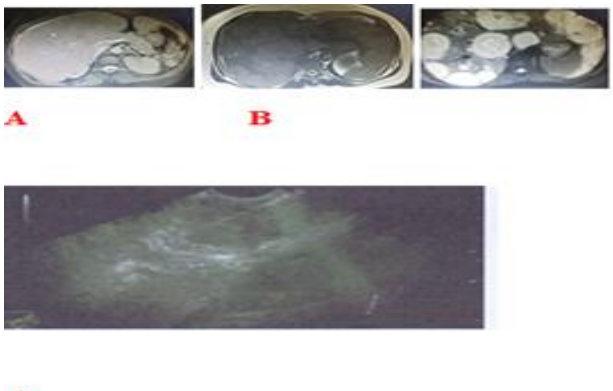

Figure 1. C.T. scan showed multiple hypodense ill-defined masses in the liver parenchyma(A), M.R.I. showed multiple low T1, high T2 lesions in the liver parenchyma (B), and E.U.S. showed 29*25mm hypoechoic mass in pancreatic body(C).

Upon consultation with the gastroenterologist, abdominal sonography revealed a liver larger than average size, mild ascites, and multiple heterogeneous lesions with different sizes (maximal size 50-60 mm). It recommended an abdominopelvic triphasic C.T. scan for further evaluation.

C.T. scan showed multiple hypodense ill-defined masses in the liver parenchyma, the largest ones measuring 108*62mm, respectively, in the right lobe of the liver **(Figure 1A);** reason for metastatic liver disease colonoscopy and endoscopy were performed, and findings were normal.

Diagnostic examinations were carried out to exclude other possible causes of hypoglycemia. Blood glucose level was 41 mg/dL with inappropriately high plasma insulin and C-peptide levels; 82.2 μIU/mL (2.6–25 μIU/mL) and 3.02 pmol/L (0.15–0.30 pmol/L) and level of plasma sulfonylurea with liquid chromatography/tandem mass spectrometry(LC/MS-MS) methodology was negative, respectively. After confirming the diagnosis of endogenous autonomous hyperinsulinism, additional research to look for an insulinoma was begun.

Given the high suspicion of malignant insulinoma according to the clinical presentation of hypoglycemia and findings on abdominal C.T. scan, Magnetic resonance imaging (M.R.I.) was ordered, which

revealed the most significant a lesion in the IV segment of the liver with a size of 66 x 122 mm" should be stated. low T1 /High T2 signal. The lesion in the pancreatic tail measured 40*25 mm, which demonstrated mild enhancement; overall findings are more in favor of PNET **(Figure 1B)**.

Endoscopic ultrasonography (E.U.S.)/F.N.A. was done to determine the diagnosis, and the impression was that the pancreatic body and tail mass — PNET is suggestive **(Figure 1C)**.

The pathology report showed well-differentiated neuroendocrine tumor grade I; immunohistochemical staining (I.H.C.) reported synaptophysin (weakly positive), chromogranin (strongly positive), pan-ck (positive), and Ki67 (2% positive) **(Figure 2).**

Histological assessment of the hepatic lesions was reported as neuroendocrine tumor metastases with positive immunohistochemical staining for CK7, CD56, and C.E.A. weakly positive **(Figure 3).**

The subsequent experiments included no lungs, bone, or brain metastases being detected, and an Indium-111 pentetreotide scan (OctreoScan) showed intense radiotracer uptake in the pancreatic region and multifocal hepatic lesions. **(Figure 4 A)**

The case was possibly diagnosed with multiple endocrine neoplasia type 1 (MEN-1), but no related symptoms of the pituitary or parathyroid were noted.

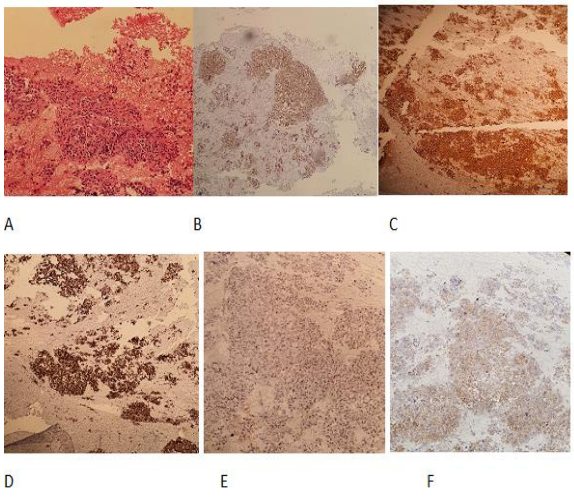

Figure 2. Pathology report of pancreatic mass showed well-differentiated neuroendocrine tumor grade I; H&E staining, ×100 (A) (A) and immunohistochemical staining (I.H.C.) reported synaptophysin weakly positive(B), chromogranin strongly positive(C), pan-ck positive(D), Ki67,2% positive(E) and Betacatenin Negative (F).

Furthermore, investigations were not accompanied by MEN1. Pituitary gland MRI and Ultrasound of the parathyroid and serum level of parathyroid hormone (PTH; 50 pg/mL, normal range: 12–88 pg/mL), growth hormone, prolactin, and calcium were normal.

Discussions regarding the case were performed at our multidisciplinary tumor board, and she was considered inoperable, and medical treatment was chosen.

She was referred to the oncologist for the progressive symptoms; the patient was a candidate for treatment with diazoxide 50 – 100 mg daily. Sandostatin L.A.R. (octreotide long-acting release) 30 mg every three weeks was administered for two months. However, no clinical improvement was observed, and frequent life-threatening hypoglycemic attacks occurred. Subsequently, Ga-68-DOTATATE –PET/CT SCAN was taken, which showed an avid tumoral mass in the pancreatic tail compatible with the known primary tumor and metastatic lesions in both hepatic lobes **(Figure 4 B** and **C).**

The patient could be considered for Lutetium-177 therapy and a further line of treatment, including Peptide Receptor Radionuclide Therapy (PRRT) associated with an S.S.A. Two months after PRRT, a whole-body scan with 177Lu-DOTATATE was performed, and that impression corresponded to multiple somatostatins –avid lesions in the liver, pancreas, and ascites/peritoneal seeding. Because of no clinical improvement and hypoglycemic episodes, the patient discounted PRRT, and unfortunately, the patient refused the treatment by everolimus and did not pursue treatment. The patient's clinical condition was progressive, and liver enzymes were increasing. The patient had encountered deteriorative clinical features

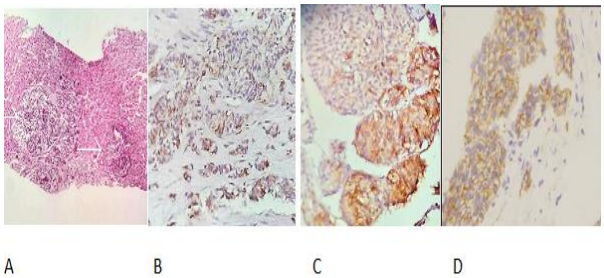

Figure 3. Pathologic specimens of liver metastases, Nests of neoplastic epithelial cells with hyperchromatic nuclei and clear cytoplasms invading liver tissue, H&E staining, ×100 (A), and positive immunohistochemical staining for CK7 is weakly positive (B) and C.E.A. weakly positive (C) and CD56 (D).

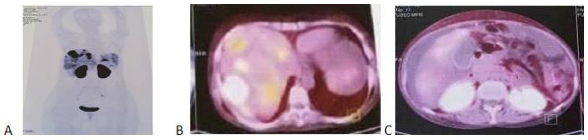

Figure 4. OctreoScan showed intense radiotracer uptake in the pancreatic region and multifocal hepatic lesions (A), and Ga-68-DOTATATE –PET/CT SCAN showed an avid tumoral mass in the pancreatic tail compatible with the known primary tumor, metastatic lesions in both hepatic lobes (B, C).

due to hepatic failure. Unfortunately, she died six months after the initial diagnosis of pneumonia and respiratory failure resulting from COVID-19.

Discussion

The present study described a rare case of pNET with an initial presentation of symptomatic hypoglycemic attack and severe hepatic dysfunction. Notably, the first step in managing acute and severe hypoglycemia is to treat it. Clinical and paraclinical findings are strongly suggestive of malignant insulinoma and liver metastasis.

Insulinoma is the most frequent functional pNET and regularly develops as a single, small (usually 2 cm diameter), benign, and sporadic tumor, which is derived from islet beta cells of the pancreas[5,6]. One such pNET, the insulinoma, presents with a composite of classic symptoms termed Whipple's Triad: fasting hypoglycemia (glucose < 50 mg/dL), symptoms during the hypoglycemic episodes, and relief of symptoms with the administration of glucose[7].

The diagnosis of this disease is majorly dependent on clinical symptoms of hypoglycemia and the findings of laboratory tests and imaging examinations. The patient in our case was one of those approximately 1 to 3 per 10 million individuals found to have malignant insulinoma. In our case, highlighted symptoms in the presence of malignant insulinoma are characterized by non-specific presentations of fatigue, weight loss, hepatomegaly, and symptoms associated with metastasis to those organs.

Treating malignant insulinoma is a great challenge; surgery was the initial treatment that was chosen. According to previous research, in cases with unresectable liver metastases, primary tumor removal may result in an enhancement in the survival rate[8-10].

A recent study by Mohammad Zarei et al. reported that A non-secretory malignant insulinoma: a case report. The patient was a 62- year-old Persian female. Over the she had developed increased abdominal mass, dizziness, weakness, and fatigue. After the surgical operation, chemotherapy was given to the patient. Treatment with cisplatin and etoposide was commenced in a 4-month course. As a result, chemotherapy plays an important role in the management of insulinoma[11].

In our case, managing treatment was associated with challenges for the hypoglycemic syndrome and aggressive tumor growth because of unresectable tumors.

Medical therapy is indicated to control insulin hypersecretion and hypoglycemia. Diazoxide is the most frequently utilized first-line treatment for controlling hormonal syndromes. An agent that suppresses insulin release of insulinoma cells through opening ATP-sensitive potassium channels and is effective in preventing hypoglycemia[12].

The S.S.A. has been shown to be an efficient treatment for differentiated pNET. It is observed to be effective in controlling both tumors and symptoms and constitutes a substitute for diazoxide in second-line treatment[13].

The National Comprehensive Cancer Network's 2020 guidelines recommend consideration of lanreotide or octreotide, somatostatin analogs, as treatment options for non-resectable, symptomatic, metastatic neuroendocrine tumors of the pancreas[14].

In this case, despite the significant absorption seen in the malignant intra-abdominal lesions during OctreoScan, the hormonal response to octreotide treatment was unsatisfactory.

Some individuals with malignant insulinomas have shown considerable improvements following the use of other anticancer treatments, such as hepatic artery embolization and peptide receptor radionuclide therapy (PRRT), and these may be attempted in case of the progression of the disease[13,15].

A recent study by Verma, Priyanka MBBS et al.reported that Peptide receptor radionuclide therapy is a promising targeted radionuclide therapy in patients of metastatic insulinomas that can result in reduced tumor burden and improved quality of life, particularly those who fail the conventional treatment modalities as seen in the present case[16].

Peptide receptor radionuclide therapy is an efficient

therapeutic option for the improvement of hormonal syndromes and the general reduction or stability of tumor burden in N.E.T.s. However, even if promising, the information regarding malignant insulinoma is minimal but, in some cases, results in a complete or limited reduction of hypoglycemic episodes[6].

A recent study by Ebru Yilmaz et al. reported that Survival rates of patients with neuroendocrine tumors with liver-dominant metastatic diseases are improved by individualized selective internal radiotherapy, peptide receptor radionuclide treatments, and their combinations[17].

The antiproliferative effect of everolimus and sunitinib prolongs progression-free survival in patients with an unresectable or metastatic insulinoma. In case of failure, chemotherapy protocol with streptozotocin, doxorubicin, and/or 5-fluorouracil, or cisplatin with etoposide for malignant insulinoma should be considered[18].

In cases of malignant insulinoma with refractory hypoglycemia, everolimus is recommended. Everolimus has a glycemic control impact in addition to an anticancer effect, which considerably improves the prognosis of pNET[12,19].

A similar case report by Qing Liu1 et al. reported the process of diagnosing and treating a sporadic case of malignant insulinoma with liver metastasis derived from the ectopic pancreas, which underwent treatment with everolimus and S.S.A. Additionally, partial tumor responses were obtained and stabilized, but because of the recurring side effects, everolimus was discontinued after nearly nine months of use, and maintenance therapy was with S.S.A. alone on a monthly use[20].

Another case report by Emre Bozkirli et al. presents a resistant case of inoperable malignant insulinoma that underwent treatment with many medications and interventions, which included S.S.A., Yttrium-90 radioembolization, everolimus, radiotherapy, and chemoembolization. Notably, the most favorable response regarding symptom control was observed following the use of everolimus, which was reported to close blood glucose monitoring[21].

In this case, most of the time, the patient refused to be treated by everolimus with therapeutic strategies based on the organ involved in pNET, which are not the same. However, these patients utilized S.S.A., PRRT, everolimus, and chemoembolization. Nevertheless, studies with more cases are needed to support these therapies[21].

Unfortunately, in the studied case, because of late patient referral and socioeconomic conditions and associated COVID-19 disease, evaluating other treatments, such as everolimus and others, for this patient was impossible, resulting in death.

Conclusion

This case report highlighted uncommon findings associated with malignant insulinomas, such as severe hepatic dysfunction and hypoglycemia, as initial presentations, which followed a poor progressive clinical course. Proposedly, rapid diagnosis and programmed treatments are warranted.

Acknowledgment

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