

Persistent hypoglycemia in the setting of metastatic malignant insulinoma to the liver treated with chemoembolization and bland embolization

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Abstract

We are describing a patient with malignant insulinoma and unusual clinical and pathological features. The patient presented late in the course of the disease with history of abdominal pain and was found to have large tumor of the pancreas and metastasis to the liver. Also, he presented with acute diarrhea which is not a feature of Insulinoma. During the hospital stay the patient had severe hypoglycemia with very inappropriately high to the low blood glucose levels of Insulin, C-peptide and Proinsulin. On biopsy of the tumor it was found to be neuroendocrine tumor, but staining's for Insulin were negative. The patient was treated with surgical resection of the distal pancreas when the insulinoma was located, splenectomy, cholecystectomy and appendectomy. Also, chemoembolization and embolization of the metastatic tumors of the liver were done and patient's hypoglycemia was treated with Diazoxide and short course of Steroids and Octreotide.

We underscore the need of combined clinical, laboratory, radiological and pathological approach while diagnosing malignant Insulinoma.

Keywords: Malignant; Insulinoma; Hypoglycemia; Chemoembolization; Neuroendocrine tumor; Whipple's triad

1. Introduction

Insulinomas are rare neuroendocrine tumors with a reported incidence of 4 cases per million per year [1]. They are most common in people over 50 years of age and in females [2]. The majority (>90%) of insulinomas are solitary, benign, and less than 2 cm in diameter. Malignant insulinomas are extremely rare and make up less than 10% of all insulinomas [3]. Insulinomas have been found to be evenly distributed throughout the pancreas. Metastatic disease is most common to the liver, local tissues and blood vessels, and abdominal lymph nodes and rarely to the bones [3].

The diagnostic criteria of hypoglycemia can be made by demonstration of the Whipple's Triad which consists of fasting hypoglycemia (plasma glucose < 50 mg/dL), symptoms of hypoglycemia at the time of low blood glucose, and prompt relief of symptoms following the administration of glucose to treat hypoglycemia [3].

The hypoglycemic symptoms might be- Adrenergic-tremor, palpitations, anxiety and cholinergic-sweating, hunger, paresthesia or Neuroglycopenic - cognitive impairment, behavioral changes, psychomotor abnormalities, Dizziness, amnesia, impaired concentration, seizures and coma as well as brain death.

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When determining the cause of hypoglycemia, we need to exclude pseudo hypoglycemia as well as other causes for low plasma blood sugar- medications, critical illness, and cortisol, Growth hormone deficiency, and Glucagon and epinephrine deficiency, non-islet cell tumors in patients who are sick. In seemingly non ill patients' endogenous hypoglycemia needs to be looked for. Usual causes might be Insulinoma, functional beta cell disorders- non insulinoma pancreatogenous hypoglycemia or post gastric bypass hypoglycemia/Nesidioblastosis/, Insulin autoimmune hypoglycemia due to antibodies to Insulin or Insulin receptor which are very rare.

Further testing is needed if we suspect Insulinoma which presents usually with fasting hypoglycemia and the patients have neuroglycopenic symptoms. We perform to prove that the patients have insulinoma or other causes of hypoglycemia while the patient is not eating 72-hour fasting test. Usually in Insulinoma the Whipple's triad can be demonstrated in 43% of the patient after 12- hours of fast, in 67 % of patients in 24- hours of fast and in 95% of patients after 48- hours of fast. During hypoglycemia with plasma blood glucose less than 55 mg/dl if the patient has Insulinoma we can demonstrate insulin greater than 3 mIU/L, C-peptide greater than 0.2 ng/ml, and a proinsulin greater than 5 pmol/L, beta – hydroxybutyrate less than 2.7 nmol/l and after administration intravenously of 1 mg Glucagon in 30 – minutes the plasma blood glucose increases with more than 25 mg/dl. There should be no evidence of anti- insulin antibodies and no evidence of sulfonylurea use or glinide's use [4].

Localization of the insulinoma can be done through noninvasive studies (abdominal ultrasound, computed tomography, magnetic resonance imaging) with invasive studies (endoscopic ultrasonography and selective arterial calcium stimulation with hepatic venous sampling) with sensitivity approaching 100% in detection of Insulinoma in these combined approach [4, 5].

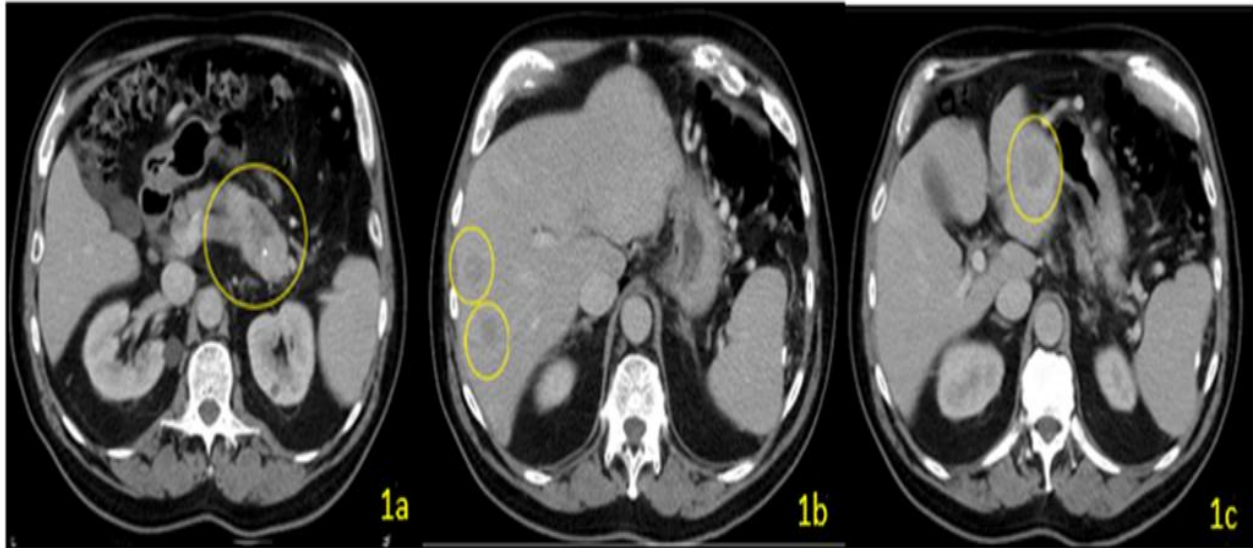
In hepatic of Insulin which is done very rarely if all other tests cannot localize Insulinoma the differentiation between Insulinoma and functional beta cell disorders- non insulinoma pancreatogenous hypoglycemia or post gastric bypass hypoglycemia can be done. After injection of calcium gluconate in the splenic artery, superior mesenteric artery or gastroduodenal artery there is increment in hepatic vein insulin 2-3 times higher than baseline. In Insulinoma this is observed after injection of calcium gluconate in only one of the arteries while in functional beta cell disorders by injection of calcium in all three arteries. Sometimes localization of Insulinoma is made by ultrasound during operation, but now with positron emission tomography with the radiotracer 68 Gallium-(Tyr3)-octreotide, the non- invasive localization of the Insulinoma become the preferred approach [6].

Surgical intervention is the only curative treatment for insulinomas. In patients with malignant Insulinomas with unresectable metastatic disease a combination of medical therapy and interventional procedures can be used to prevent hypoglycemia and control tumor growth and spread. Octreotide, diazoxide, and lanreotide can be used as medical therapy to prevent symptomatic hypoglycemia, but the best long-term results have been with diazoxide. Interventional treatment depends on the extent of metastasis and size of lesions. These procedures include hepatic resection, hepatic artery embolization, chemoembolization, radiofrequency ablation, and chemotherapy. The metastasis from malignant Insulinomas is usually in the locoregional lymph nodes, liver and rarely in other locations like bones [7].

2. Case Presentation

Our patient was a 72-year-old male with a medical history significant for hypertension and obstructive sleep apnea who presented to the emergency department with 4-day history of right lower quadrant abdominal pain and diarrhea. Vital signs on admission showed an oxygen saturation of 95% on ambient air, respiratory rate of 18 breaths per min, heart rate of 97 beats per min, and a temperature of 36.6°C. Initial laboratory studies including complete blood count (CBC) and comprehensive metabolic panel (CMP) were within normal limits with the exception of aspartate aminotransferase (AST) 48 IU/L (Normal: 15-37 IU/L). Computed tomography (CT) of the abdomen and pelvis with intravenous (IV) contrast demonstrated a 6 cm mass in the tail of the pancreas [figure 1a] with thrombosis of the adjacent splenic vein, multiple hypodense liver lesions with imaging characteristics of metastatic disease [figure 1b]. The largest metastatic lesion was 3 cm mass within the left hepatic lobe [figure 1c]. Ultrasound guided liver biopsy was performed and histopathology was consistent with metastatic carcinoma with neuroendocrine features.

Gastroenterology was consulted and patient underwent endoscopic ultrasound (EUS) with fine needle aspiration (FNA) of pancreatic tail mass which demonstrated a well-differentiated neuroendocrine tumor. General surgery was consulted and patient underwent exploratory laparotomy with distal pancreatectomy, splenectomy, cholecystectomy, and appendectomy. Surgical pathology of appendix and gallbladder showed chronic inflammation with no malignancy identified. Surgical pathology of the spleen and pancreas was consistent with a well-differentiated neuroendocrine tumor. Surgical specimens did not stain for insulin.



1a. axial image showing a large 6 cm mass within the tail of the pancreas; 1b. axial image showing multiple hypodense and non-cystic lesions throughout the right lobe of the liver; 1c axial image showing a large 3 cm mass within the left lobe of the liver

Figure 1 Ct abdomen/pelvis with IV contrast

Hematology-Oncology specialist was consulted.

Laboratory work-up while the patient was fasting with plasma glucose level of less than 55 mg/dl and with symptomatic hypoglycemia showed significant fasting proinsulin level of 2265 pmol/L which was very high (normal was less than 5 pmol/L), fasting C- Peptide of 8.3 ng/ml also very high (normal was less than 0.2 ng/mL) and Insulin level of 15mIU/L (normal < 3 mIU/L) if the blood glucose is less than 55 mg/dl like in ours patient.

Patient underwent a Tran's arterial chemoembolization with doxorubicin and gel foam of the liver segments 2 and 3 and gel foam bland embolization of the remaining of the liver metastasis. Patient was discharged home. The treatment on discharge was subcutaneous octreotide, prednisone, and diazoxide, with plan to follow up as outpatient with the oncology and endocrinology specialists.

Five months later, patient returned to the hospital for persistent fasting and post prandial hypoglycemia measured at home. The capillary blood glucose at home was frequently less than 45 mg/dl. He reported also weakness and fatigue. The patient denied nausea, vomiting, diarrhea, headaches, vision changes, palpitations, or diaphoresis. On admission, serum blood glucose was 69 mg/dL with point of care glucose 27 mg/dL.

Vital signs were otherwise stable. Patient was started on Dextrose 10 % In Water (D10W) drip and an octreotide drip.

Hematology-Oncology and Endocrinology specialists were consulted for further management. Due to persistent hypoglycemia and inability to wean off the D10W drip, the patient was evaluated for inpatient chemoembolization. Pre-embolization, CT angiography (CTA) of the abdomen and pelvis demonstrated multiple heterogeneous lesions throughout the liver with the largest being 5.7 x 6.7 cm, suggestive of metastatic disease.

Aortogram was done followed by transcutaneous bland embolization of the liver lesions.

Patient was transferred to the intensive care unit (ICU) for frequent blood sugar monitoring. Pre-procedural glucose ranged 62-102 mg/dL while on D10W and octreotide drip.

Post-procedural plasma blood glucose was 114 mg/d-120 mg/dl without D10W and Octreotide drip. Throughout the hospital course, he continued to demonstrate stable blood glucose measurements of 140-190 mg/dL. Patient was ultimately discharged on Diaz oxide with outpatient follow-up with hematology-oncology and endocrinology specialists.

3. Discussion

Malignant or metastatic insulinoma is a rare condition. Patients with malignant insulinoma present with two fundamental challenges to the managing clinician.

The first is that the tumor is, by definition, metastatic.

The second is the unregulated secretion of insulin and proinsulin-related products that leads to severe hypoglycemia.

In contrast to other islet cell tumors such as gastrinoma (Zollinger-Ellison syndrome) and vasoactive intestinal peptidoma (VIPoma), most insulinomas are believed to be benign. Only 5–12% of reported cases of insulinoma are malignant [7].

Most patients with malignant insulinoma have lymph node or liver metastasis and only rarely have metastasis to other sites such as bone [7].

In spite of therapies in these patients that have been used with some short-term benefits including surgery, chemotherapy, bland embolization, chemoembolization, radiofrequency ablation, and somatostatin analogs the prognosis of these patients is relatively poor with a median survival period of approximately 2 years.

The patient we described presented with late manifestation of malignant Insulinoma like abdominal pain. Other unusual presentation was the diarrhea which usually is absent in Insulinomas. The diagnosis was made by finding low BS associated with very high levels of Insulin, C- peptide, Proinsulin while the patient was fasting with plasma blood sugar less than 55 mg/dl as well as the classical abdominal CT findings suggestive of metastatic insulinoma.

The pathological report was suggestive of neuroendocrine tumor although the staining was negative for Insulin. The classical clinical and laboratory picture suggested Insulinoma as a cause of the neuroendocrine tumor of the pancreas irrespective of the negative pathology staining's.

The first challenge in treating the patients with malignant Insulinoma is to identify patients at risk for the more aggressive forms of the disease. To our knowledge, there currently are no histological criteria that define malignancy other than the presence of disease at a metastatic site.

There were no distinguishing morphologic features of the pancreatic tumor that predicted a subsequent metastasis.

Our patient had inappropriate elevation of Insulin, C-peptide and proinsulin levels at the time of diagnosis, while the blood glucose was less than 55 mg/dl and the patient was symptomatic, but the more aggressive and less aggressive groups could not be distinguished nor could either be distinguished from the more common benign insulinoma. Metastasis to the liver is usually but not always are associated with poor prognosis as in our patient.

Currently there are no predictive factors to determine patients at risk for subsequent metastatic disease and there are no predicative factors to suggest how aggressive the disease may be. Also few patients (approximately 2%) diagnosed with benign insulinomas will later present with metastatic disease.

Diazoxide therapy for control of hypoglycemia has had the greatest long-term benefit [7, 8,9].

Some patients have gastrointestinal intolerance to the drug and in very high doses it may produce anorexia. We have found that a small initial dose with an increase of ≤ 300 –400 mg per day over 3–4 weeks is the most effective way to initiate and maintain therapy. All other forms of therapy have relatively short-term benefit and most, such as chemotherapy regimens, are toxic and of little benefit. Of all approaches available, embolization and chemoembolization may have the greatest benefit next to diazoxide.

This is why in our patient besides surgical treatment of Insulinoma- distal pancreatectomy we utilized bland embolization and Chemoembolization of the metastasis to the liver and control of the blood sugar with Diazoxide, Prednisone and Octreotide after the first discharge from the hospital.

The role of Octreotide in treatment of malignant insulinoma associated hypoglycemia is debatable.

After the second discharge from the hospital, we used only Diazoxide which has been the only drug with excellent track record for long term treatment of hypoglycemia due to Insulinoma in the literature [7, 8,9].

We wanted to present this case of malignant Insulinoma who presented to us with late manifestation of metastatic disease. Also, unusual feature of our patient was the presence of diarrhea and lack of staining for insulin on pathological specimen which was suggestive of neuroendocrine tumor. The clinical, radiological and laboratory picture suggested the diagnosis of malignant Insulinoma.

This underscores the need of combined clinical, laboratory, radiological and pathological approach while making the diagnosis of malignant insulinoma [7].

4. Conclusion

This case report of late unusual clinical presentation of malignant Insulinoma shows that we need to place in our differential diagnosis of low blood sugar not only Insulinoma, but think that although rarely it might be malignant. Also, malignant Insulinoma might present rarely late with leading symptoms of abdominal pain due to metastasis in the liver as in our case. The diarrhea which the patient presented with was acute, probably due to viral disease, but also it was very unusual to be associated with malignant Insulinoma. Pathological staining of the tumor confirmed that this was neuroendocrine one, but was also negative for Insulin. The clinical and laboratory picture confirmed the diagnosis.

The contribution of our case to the knowledge of the physicians is to have in differential diagnosis malignant insulinoma of nonspecific abdominal pain, think that while fasting and post prandial hypoglycemia might be related to Insulinoma which might be rarely malignant and use combined clinical, pathological, laboratory and radiological approach in diagnosis of this rare disease.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest to the authors of this manuscript

Statement of informed consent

Informed consent was obtained from all individual participants included in the study

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