Case Report *Olgu Sunumu*

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A Rare Cause of Hypoglycemia in a Diabetic Patient: Malign Metastatic Insulinoma

Diyabetik Bir Hastada Nadir Bir Hipoglisemi Sebebi: Malign Metastatik İnsulinoma

Emin Murat Akbaş, Habib Bilen, Adem Güngör, İlyas Çapoğlu*, Hümeyra Başçi**

Atatürk University Faculty of Medicine, Department of Endocrinology and Metabolism Diseases, Erzurum, Turkey
*Erzincan University Faculty of Medicine, Department of Endocrinology and Metabolism Diseases, Erzincan, Turkey
**Atatürk University, Faculty of Medicine, Department of Internal Medicine, Erzurum, Turkey

Abstract

The occurrence of metastatic insulinoma in a patient with pre-existing diabetes is extremely rare. We report the case of a diabetic patient who had frequent hypoglycemic episodes, apparently related to metastatic insulinoma. A 47-year-old woman with type 2 diabetes mellitus who had been treated with a sulfonylurea for 10 years began experiencing frequent episodes of hypoglycemia even after complete withdrawal of the hypoglycemic agent. Endogenous hyperinsulinism was found using a prolonged fasting test. Computed tomography identified a pancreatic tumor with metastatic liver lesions and peripancreatic lymphadenopathies. Ultrasound-guided hepatic mass biopsy was performed and the pathology examination of the tumor demonstrated a neuroendocrine tumor. The patient refused surgery; octreotide (10 mg) was administered. A few days later, the patient had no further episodes of hypoglycemia. Although the coincidence of insulinoma and diabetes is extremely rare, after excluding common reasons for hypoglycemia in diabetic patients, insulinoma must be considered. *Turk Jem 2012; 16: 82-4*

Key words: Diabetes, insulinoma, hypoglycemia

Özet

Diyabeti olan bir hastada, metastatik insülinoma görülmesi oldukça nadirdir. Tarafımızdan sık görülen hipoglisemi ataklarının, metastatik insülinomaya bağlı olduğu, aşikâr şekilde ortaya konulan bir diyabetik hasta rapor edildi. Kırk yedi yaşında, tip 2 diabetes mellitus tanısı almış, on yıldır tedavi olarak sulfanilüre kullanan bayan hasta, hipoglisemik ajanı tamamen kesmesine rağmen, hipoglisemi episodları tarif etmekteydi. Uzamış açlık testi ile endojen hiperinsülinizm tespit edildi. Bilgisayarlı tomografi ile, karaciğer metastazları, peripankreatik lenfadenopatiler ve pankreatik tümör tespit edildi. Ultrason eşliğinde hepatik kütle biyopsisi yapıldı ve patolojik incelemesi sonucunda nöroendokrin tümör rapor edildi. Hastanın cerrahiyi reddetmesi üzerine octreotid (10 mg) uygulandı. Uygulamadan bir kaç gün sonra, hastada bir daha hipoglisemi atağı yaşanmadı. Her ne kadar, insulinoma ve diyabet birlikteliği nadir de olsa, hipoglisemi için sık görülen nedenler dışlandıktan sonra, insulinoma akılda tutulmalıdır. *Türk Jem 2012; 16: 82-4*

Anahtar kelimeler: Diyabet, insülinoma, hipoglisemi

Introduction

Although insulinomas are very rare tumors, they are the most common functioning pancreatic neuroendocrine neoplasms (1,2). The association of diabetes mellitus and insulinoma is very rare; in fact, only a few cases of insulinoma associated with diabetes have been reported and only two of these cases (one with type 2 diabetes and one with type 1 diabetes) were malignant or metastatic (3,4). In our knowledge this is one of the few malign insulinoma cases reported in type 2 diabetes.

History and Exemination

A 47-year-old woman with type 2 diabetes was admitted to the endocrinology department for evaluation of frequent hypoglycemic episodes. Her diabetes had been diagnosed in 2000 and was

Address for Correspondence/Yazışma Adresi: Emin Murat Akbaş MD, Atatürk University Faculty of Medicine, Department of Endocrinology and Metabolic Diseases, Erzurum, Turkey
Gsm: +90 532 507 93 05 E-mail: dremakbas@hotmail.com **Recevied/Geliş Tarihi:** 05.02.2012 **Accepted/Kabul Tarihi:** 26.10.2012

treated with glipizide (10 mg) once a day. For 2 months prior to admission, she had been experiencing episodes of hypoglycemia, and she had discontinued her oral antidiabetic drugs. However, she continued to have frequent hypoglycemic episodes after complete withdrawal of the hypoglycemic agent.

Physical examination was unremarkable except for obesity. Her weight was 77 kg and height was 159 cm. Her body mass index was 30.45 kg/m^2 and she stated that she gained nearly ten kilograms in the last few months.

The episodes typically occurred in the morning, just after waking. The biochemical examinations in fasting frequently showed hypoglycemia. The patient's glycosylated hemoglobin (A1c) was 7.4%. During the 72-hour fasting test, neuroglycopenic symptoms occurred; the serum glucose level was 28 mg/dl on the first day after a 14-hour fast. Serum insulin and c-peptide levels were 193.6 µu/mL and 12 ng/mL, respectively. Abdominal computed tomography (CT) scan was done and demonstrated an approximately 5-cm mass in the head region of the pancreas and many masses in the liver that were highly suspicious for metastases and there were multiple peripancreatic lenfadenopathies (Figure 1,2). An ultrasound-guided hepatic mass biopsy was performed and the pathology revealed an endocrine tumor consistent with insulinoma. At the pathological examination, no mitotic activity was observed and Ki-67 proliferation index was "0". Cytological atypia, necrosis and angioinvasion were not seen. The tumor size and the depth of tumor invasion could not be evaluated. After considering c-peptide levels, imaging and pathology data, other causes of hypoglycemia were ruled out. All findings were compatible with the diagnosis of malignant metastatic insulinoma.

Figure 1. Abdominal CT scan demonstrated many masses in the liver that were highly suspicious for metastases.

Figure 2. Abdominal CT scan demonstrated approximately 5 cm mass in the head region of the pancreas

The patient refused surgery and was treated with 10 mg of a long-acting, repeatable formulation of octreotide. Over the next few days, she showed rapid and progressive improvement. After two additional doses of octreotid, she had no further hypoglycemic episodes and her A1c was 11.3%. After elevation of HbA1c, low dose of insulin was started.

Investigation

Hypoglycemia is a common clinical entity and is most frequently due to a complication of diabetes treatment (4,5). When a patient with diabetes presents with hypoglycemia, the most common explanations are overtreatment, inadequate food intake, or increased physical activity. However, with an atypical, undetermined etiology of hypoglycemia, rare causes must also be considered. Our patient had hyperinsulinemic hypoglycemia even after complete withdrawal of the hypoglycemic agent. The differential diagnoses of hyperinsulinemic hypoglycemia include familial persistent hyperinsulinemic hypoglycemia, primary islet-cell hyperplasia, noninsulinoma pancreatogenous hypoglycemic syndrome, insulinoma, and factitious hypoglycemia (6). Other causes of hypoglycemia were ruled out due to c-peptide levels, imaging and pathology data. Our patient's findings clearly fulfilled the criteria for insulinoma, which was demonstrated by CT.

Insulinoma is the most common cause of endogenous hyperinsulinemic hypoglycemia in adults. Its incidence is estimated to be 1-4 cases per million people per year (2). Symptoms may be present from 1 month to as long as several decades prior to the diagnosis (1). Most insulinomas are sporadic in their origin. Approximately 10% are malignant, and 4-8% are associated with Multiple endocrine neoplasia type 1 (MEN-1) syndrome (2).The highest incidence is in people between 40 and 60 years of age, and females show a slight predominance over males (7).

The diagnosis of insulinoma depends on the exclusion of other causes of hypoglycemia, such as the surreptitious administration of insulin or oral antidiabetic agents, and the presence of inappropriately elevated plasma insulin and C-peptide levels with hypoglycemia (4). Most of the insulinomas are intrapancreatic, benign, and solitary (1), therefore, they have an excellent prognosis after surgical resection (1).

Generally, ultrasound, CT, angiography, and transhepatic portal venous sampling are used in the preoperative localization of such tumors with various rates of accuracy of localization reported by investigators (1). The management involves a more radical surgical approach for the treatment of tumor masses and liver metastases by embolization or thermoablation (8,9). In addition, the use of radiopeptide therapy is increasingly advocated (9).

For patients who are not good surgical candidates, who refuse surgery, or whose insulinoma was missed during surgery, as well as for patients with metastatic disease, medical therapy should be

attempted. The goal of medical therapy is to prevent symptomatic hypoglycemia. Medications that have been used for this purpose include diazoxide, verapamil, phenytoin, and octreotide (1,9,10). Diazoxide diminishes insulin secretion and is the most effective drug for controlling hypoglycemia. Octreotide, the somatostatin analog, is also a common treatment for patients with unresectable tumors (10). In our patient, octreotide completely resolved the hypoglycemia and the patient had a mild hyperglycemic metabolic state.

Conclusions

Misdiagnosis of insulinoma is common. Although the coincidence of insulinoma and diabetes is extremely rare, after excluding the common reasons for hypoglycemia in diabetic patients, insulinoma should be considered.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material. Written and informed consent was obtained from the patient for publication of this case report along with images.

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