Insulinoma in a Patient with Type 2 Diabetes Mellitus

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Abstract- Insulinoma in a patient with pre-existing diabetes is extremely rare (1). Only a small number of cases have been reported all over the world (2). We report a case of insulinoma in a patient with type 2 diabetes. A 63-year-old female was diagnosed to have diabetes mellitus six years ago, she was given metformin and sulphonylurea to control her glycemia, she had adequate glycemic control for many years, but thereafter, the patient has experienced hypoglycemia after cessation of the treatment since 8 months ago and was hospitalized for further examination, endogenous hypoglycemia was confirmed and the level of serum insulin and C-peptide were elevated. Endoscopic ultrasound showed a heterogeneous lesion in the head of the pancreas. Head pancreatectomy was done. In the postoperative period diabetes again developed and required oral agents for control.

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Introduction

Insulinomas are uncommon tumors with an estimated incidence of 4 cases/1 million/ year, based on population studies (1). These tumors are usually benign (90%), and nearly 60% of them occur in females who are between 40-60 years of age, these usually solitary tumours are small and 40% are less than 1 cm in diameter (11), they may occur in subjects with T2DM, but this is very rare (3), studies from the United States, Japan, and Taiwan have reported only 3 with concomitant T2DM in a combined total of 779 insulinoma patients (11-13). Occurrence of unexplained hypoglycemia in a patient with known hypoglycemic episodes in a diabetic are mostly due to excess doses of exogenous insulin /oral hypoglycemic agents coupled with a poor caloric intake and excessive unplanned physical exertion or development of nephropathy or liver disease (1-2).

We report a patient with type 2 diabetes mellitus who initially required metformin and sulfonylurea for glycemic control, later she developed recurrent episodes of hypoglycemia which persisted even after sulfonylurea and metformin were withdrawn. She was found to have hyperinsulinemic hypoglycemia suggestive of insulinoma. The endoscopic ultrasound showed a heterogeneous lesion in the head of pancreas.

The Patient underwent head pancreatectomy. In the postoperative period the hypoglycemic episodes ended, and diabetes again developed and required oral agent's control.

Case Report

A 63-year-old woman presented with recurrent episodes of weakness, palpitations, sweating since 8 month ago. Six years back she was diagnosed as a case of type 2 diabetes mellitus, and she was started on metformin 500 mg/TDS and then added glibenclamide 5 mg daily. Her HbA1c levels always were 7-8 %.

In 2013, she experienced recurrent preprandial hypoglycemic attacks and on one such episode the plasma glucose was found to be 45 mg/dl and symptoms improved by oral glucose.

The episodes of hypoglycemia continued even after sulfonylurea was withdrawn, so metformin was reduced and finally stopped but patient had episodes of giddiness, palpitations, sweating and loss of consciousness. These episodes occurred mostly in the fasting state, almost always in the morning or late in the

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evening. Hypoglycemia was documented many times during such episodes and the patient improved with intravenous dextrose.

At this time she had 6-7 kg increase in the body weight; the patient was admitted to the hospital and evaluated for hypoglycemia. Her physical exam and common laboratory tests were normal (Table 1).

Table 1. Primary Laboratory Data

Test	Result	Normal Range
TSH	2/7 mIU/L	0.27- 4.2
FBS	60 mg/dl	75-110
BUN	40 mg/dl	8-23
Cr	1.4 mg/dl	0.5-1.5
Uric Acid	5.2 mg/dl	3.4-7
TG	93 mg/dl	< 150
Chol	149 mg/dl	<200
AST	15 U/L	0-40
ALT	11 U/L	0-40
HDL	46 mg/dl	<35 High Risk
LDL	73 mg/dl	< 100
Hb A1C	4.8%	4-6
WBC	5100	4000-10000
Hg	12.3 g/dl	12-16
HCT	36.9 %	36-50
MCV	88.8	85-97
PLT	232000	140000-450000
UA	Normal	

She underwent supervised fast according to a standard protocol. After 4 hours of fasting, she developed symptoms of hypoglycemia and she had a blood sugar of 32 mg /dl (this test two times repeated). During this episode her blood sample was assessed for Insulin, C – peptide, IGF1, cortisol and sulfonylurea, urine sample was also checked for sulfonylurea (Table 2).

Table 2. Lab Data of Fasting Test

Test	Result	Reference Range
Insulin	9.9 uIU/mL	2.6-25
C- Peptide	5 ng/mL	1.1-4.4
Cortisol	7.9 mcg/dL	6.2-20
IGF1	132 ng/mL	30-196
Sulfonylurea Blood	Negative	--
Sulfonylurea Urine	Negative	--

Glucagon (1mg) was injected and then the plasma glucose in 10 – 20 and 30 minutes checked and results: 68 – 79- 85, and the level of c-peptide: 5ng/ml and insulin: 9.9 uIU/ml, then the test was ended.

The results of tests in this patient established hyperinsulinemia. Therefore Endoscopic Ultrasonography was performed in which a 14×12 mm hypoechoic lesion within the head of the pancreas was found.

The Patient underwent laparotomy, and the head of the pancreas was resected. On pathological examination well-differentiated neuroendocrine cells were seen along with insulinoma.

After surgery, the patient was well and in the immediate post-operative period the random blood sugars remained in the range of 100 -150 mg/d.

On follow up the patient developed hyperglycemia and required metformin and then glibenclamide for the management of diabetes.

Discussion

The occurrence of hypoglycemia in a diabetic patient who is being treated with hypoglycemic agents can be ascribed to some defect in design or implementation of treatment regimens, either an overdose of drugs or inadequate diet or excessive exercise. When hypoglycemia continues to occur after complete withdrawal of hypoglycemic agents, other pathogenetic mechanisms need to be considered (2-6).

Insulinoma can occur in a patient with type 2 diabetes, but the co-occurrence is extraordinarily rare (1) . Diagnosis of insulinoma is based on the exclusion of the most common causes of hypoglycaemia and demonstration of increasing both plasma insulin and C-peptide levels in the presence of low level of blood glucose (2). In our patient we have found these laboratory results after 4 hours starvation and the tumor was revealed in Endoscopic Ultrasonography.

Previous reports suggested that hyperplasia and even adenomatous transformation of the β cells of the pancreas might be induced by chronic therapy of diabetes with sulphonylureas or insulin resistance due to long lasting type 2 diabetes (14). It is now clear that insulin plays an important role in the regulation of adult β-cell mass. It seems that long lasting stimulation of insulin secretion by sulfonylureas and/ or overdose of exogenous insulin therapy might lead to uncontrolled β-cell proliferation via intracellular "insulin signaling" pathway. Recently, Beith et *al.,* have demonstrated that insulin directly stimulates β-cell proliferation, and that Raf-1 kinase is involved in this process (15).

Despite the progress in identifying regulators of β-cell expansion the mechanisms linking type 2 diabetes and insulinoma are not fully explained.

In conclusion, insulinoma must be taken into consideration as a reason for hypoglycemia in type 2 diabetes; however, the coincidence of these two diseases is extremely rare.

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