Insulinoma – An imposter

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ABSTRACT

Pancreatic endocrine tumors are rare tumors. Most common of all functional PETS is insulinoma accounting about 60 % of all the cases. It presents with symptoms of hypoglycaemia resulting from neuroglycopenia and catecholamine excess because of the excess ectopic secretion of insulin from the tumor occurring characteristically in the fasting state. Here we report two patients of insulinoma , symptomatic for long time before diagnosis was established. Both presented with symptomatic hypoglycaemic episodes. Diagnosis of insulinoma was made with demonstration of endogenous hyperinsulinemia and tumor in pancreas on computed tomography. Both the cases were managed surgically and cured completely with no recurrence of symptoms.

Key words: Insulinoma, hyperinsulinemia, hypoglycaemia, enucleation

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INTRODUCTION

Pancreatic endocrine tumors are rare tumors with annual incidence of 4 cases per annual patient year. Functional PETS usually presents clinically with symptoms due to the hormone excess state and in contrast, all the symptoms due to non-functional PETs are due to tumor per se[1]. Most common of all functional PETS is insulinoma accounting about 60 % of all the cases. It presents with symptoms of hypoglycaemia resulting from neuroglycopenia and catecholamine excess because of the excess ectopic secretion of insulin from the tumor occurring characteristically in the fasting state [2].

The majority of patients diagnosed with an insulinoma are between 30 and 60 yr of age, with women accounting for 59%. Most insulinomas are sporadic in origin. In two series, 7.6% and 12% of patients with insulinoma had multiple endocrine neoplasia type I syndrome [3]. Insulinomas are more likely to be multiple

in patients with multiple endocrine neoplasia type I. Almost all insulinomas are located within the pancreas, even though aberrant cases have been described in the duodenum, ileum, lung and cervix. Only 5-15% is malignant, therefore appropriate imaging should be performed to locate the tumor.

Surgical excision is the treatment of choice and is curative in most cases [2]. Diagnosis of this entity relies on clinical features of hypoglycemia along with laboratory tests demonstrating elevated plasma insulin levels and imaging investigations to aid in localisation. Here we report two cases of symptomatic insulinoma, recovered completely with surgery.

CASE REPORT 1

A 59 years old non diabetic female presented in emergency department with acute onset altered sensorium for 12 hrs duration. Serum glucose level measured urgently was 26mg/dl. Patient was quickly revived with dextrose 25% and 10% infusion following which she recovered completely. She also reported that she had been experiencing such episode for 6 years. Initial episodes consisted of palpitations, perspiration, tremors and were less frequent -once in 3-4 months, were of shorter duration and used to get terminated of its own.

For last 1 year, frequency had increased to 10-12 episodes / month and each episode lasting for longer duration and needed assistance at hospital. These episodes occurred more frequently when the patient was fasting and during morning hours and in few instances, episodes were averted by giving something to eat. She denied any history of galactorrhoea, headache, any drug or alcohol, intake. She was evaluated before for seizures, EEG, MRI brains were done which were normal. Though possibility of hypoglycemia was considered once after documentation of RBS of 65 mg/dl but was never evaluated further.

She was on SSRIs considering these symptoms as pseudoseizures and was taking thyroxine for hypothyroidism. Family history was insignificant. The physical examination was unremarkable. She was a well developed and well nourished woman, with no nipple discharge and a normal visual field examination. Her abdomen was soft and nontender, with no palpable masses or organomegaly. Keeping in view the possibility of spontaneous hypoglycaemia and endogenous hyperinsulinemia as the

cause, she was subjected to laboratory investigations.

Her serum insulin levels at the symptomatic hypoglycaemia (induced by keeping fasting in hospital setting) was 22 µU/ml (high) and serum C- peptide levels observed was 3.09ng/ml(high) and insulin to glucose of 0.55 (high). Diagnosis of insulinoma was made and CECT abdomen done to localize the tumor. An Ill-defined lesion of size 13x 11 mm in body of pancreas with CT attenuation of 280-310 HU on arterial phase and on post contrast iso-dense to rest of pancreas with no evidence of local invasion was seen. There was no abdominal LAP or ascitis and liver was normal. She was subjected to surgical enucleation of the tumor and well encapsulated tumor of size 1.5x 1.5 cm from body of pancreas was resected.

Histopathology of the tumor showed well encapsulated multiple tumor nodules separated by fibrous septa. Tumor nodules comprised of uniform population of round to polygonal cells having centrally located round nucleus with dense nuclear chromatin with inconspicuous nucleoli and granular eosinophilic cytoplasm. No features of malignancy were observed. Immuno-histochemisrty studies were not done. Post operative period was uneventful with no repeat hypoglycemic symptoms. She was followed up after 6months and there was no recurrence of tumor or symptoms.

CASE REPORT 2

A 42 years old non diabetic healthy male, came with complaints loss of consciousness for 3 hrs .on emergency investigations his RBS was 38 mg/dl. He was urgently revived with dextrose 25 %. Patient had been symptomatic for last 3 years with such episodes. Each episode was preceded by weird behavior, palpitations, dizziness, tremors and later loss of consciousness lasting 1-3 hrs.

They occurred more frequently when was fasting or after doing strenuous exercise/ work or during morning hours. Initial frequency was attacks 4-5 episodes / year later number of attacks increased to 10-12 attacks /years but he averted those by taking sugar solution at the onset of the symptoms. He was admitted before also for these symptoms, RBS recorded was 18mg/dl. Since then taking sugar solutions to avert the symptoms.

Further workup for hypoglycemia was not done and he was put on antiepileptic drugs which patient continued to take. But there was no reduction in the frequency of attacks. He denied any

history of drugs or alcohol intake. Clinical examination was normal. Considering the possibility of endogenous hyperinsulinemia and insulinoma as the etiology, further investigations were done. Serum insulin (measured during induced symptomatic hypoglycemia) was 4.4 μU/ml, serum C peptide was 1.76ng/ml and the ratio of insulin to glucose was 0.35. CECT abdomen revealed a well defined rounded lesion of size 22x 20mm in the body of pancreas and with marked arterial enhancement in periphery and CT attenuation of 175-195HU with hypodense component in the centre suggestive of insulinoma with no evidence of malignancy.

He was subjected to enucleation surgery and histopathology features were suggestive benign pancreatic endocrine neoplasm. Patient's symptoms resolved completely after procedure and there was no recurrence of tumor or symptoms on follow up.

DISCUSSION

Hypoglycaemia is a common medical emergency. Among hospitalised patients, it is most common in those with diabetes, but also occurs in patients with renal insufficiency, liver disease, malnutrition, congestive heart failure, sepsis or cancer. Diabetes on treatment with insulin is an important cause of hypoglycaemia among ambulatory groups. Factitious or surreptitious use of insulin or sulphonylurea drugs is probably the most common cause of hypoglycaemia among patients who do not have diabetes.

Occasionally, hypoglycaemia can be induced by endocrine tumours, commonly pancreatic tumours that secrete insulin (insulinoma) and non-islet-cell tumours that secrete insulin-like growth factors like hepatoma, adrenocortical tumors and carcinoids. Symptoms of hypoglycaemia include both neurogenic symptoms from adrenergic as well as cholinergic stimulation and neuroglycopenic symptoms as a direct result of a decrease in brain substrate [2,3,4,5].

The diagnosis of insulinoma is suggested by endogenous hyperinsulinaema in the presence of hypoglycaemia and reversal of the symptoms by administration of glucose (Whipple's triad). Insulinomas are most common functioning islet cell tumors with yearly incidence estimated to be 1 in 2, 50,000 and it accounts for > 60 % of PETS [1,2,3]. More than 80 % cases are sporadic and are solitary, benign tumors with an indolent course. These are typically

hypervascular, 90% of which measure less than 2cm and 30% measuring less than 1cm in diameter, equally distributed throughout the pancreas. Malignancy rate is around 10 % and recurrence rate is low with < 10 %.

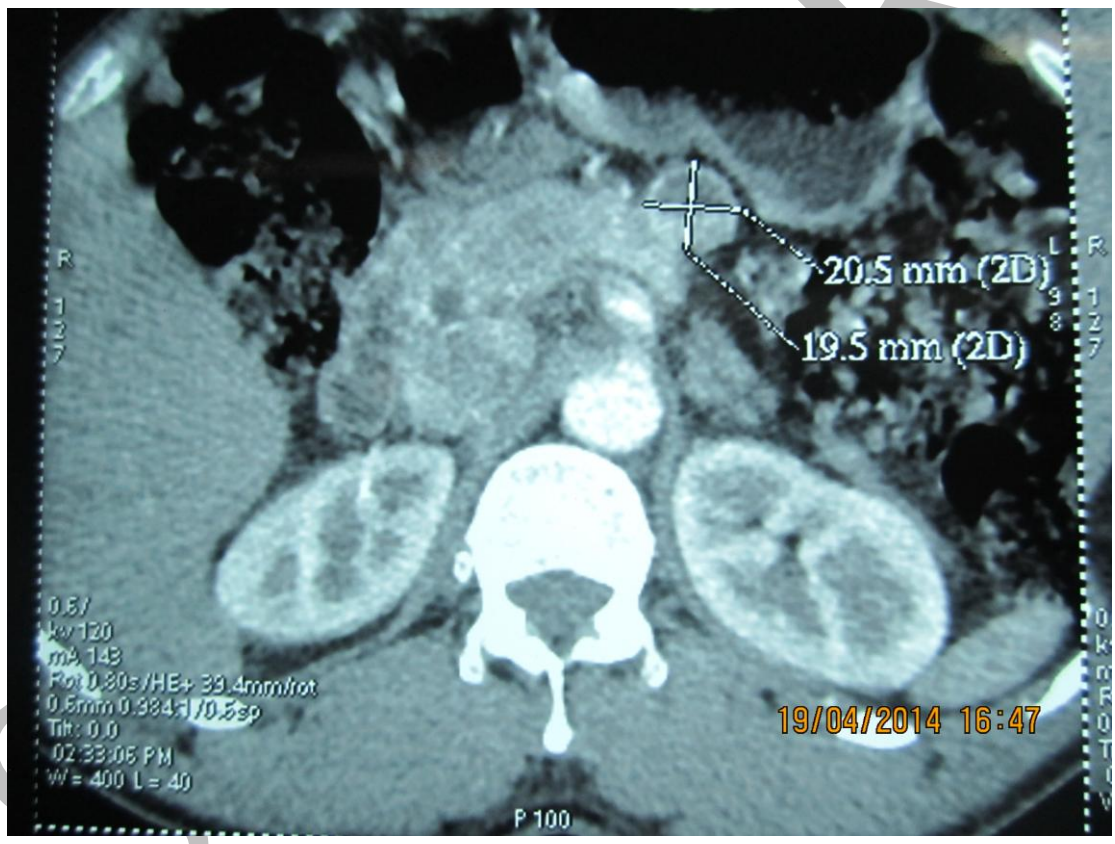
Insulinoma occurring with MEN1 tend to occur at an earlier age and comprise of one third of PETs accompanying MEN 1 patients. They occur before 40 years of age and are most common tumor seen before age 20 yrs. In contrast to sporadic cases, MEN 1 patients have multicentric , more malignant disease (25%)and higher rates of recurrence of about 21 %. Average age of presentation is 4-7 years after the symptom onset. Apart of the typical hypoglycaemic events, it may presents with neuropsychiatric manifestations in the form of abnormal behaviour, with seizures and neurological deficit and many a times patients have been misdiagnosed as having seizure disorder, psychiatric illness, stroke, syncope or hysteria[6,7,8].

There are case reports of insulinoma developing in patients with longstanding type 2 DM and subsequently wrongly diagnosed as drug induced hypoglycaemia and reduced need of antidiabetic drugs [9]. In patients with insulinoma, there is unregulated continued secretion of insulin despite a lower glucose level. In addition to this, fasting hypoglycemia in insulinoma patients is attributed to suppression of glucose production along with acceleration of glucose utilization due to endogenous hyperinsulinemic state. The suppression of glucose production can be most readily explained by a direct hepatic effect of insulin to inhibit glycogenolysis and gluconeogenesis[2,10].

Diagnostic criteria for insulinoma include a serum insulin concentration of more than 6 microU/ ml, a detectable concentration of serum C peptide, and a high proinsulin concentration, concomitant with symptoms of hypoglycaemia and blood glucose concentration of less than 45 mg per deciliter during fasting. A negative screening for sulphonylurea is required to confirm the diagnosis[5]. Once a clinical and biochemical diagnosis is established, the imaging modalities are used for localisation of tumour. Because of its high sensitivity and its ability to obtain whole body images, scintigraphy with 111In-octreotide is considered the initial imaging procedure of choice for gastroenteropancreatic tumours (including carcinoids and ICT).

However, specifically in insulinomas scintigraphy with 111In-octreotide has been shown to be less sensitive than other ICT, probably due to the lack of somatostatin receptors type 2 and the small size of the lesions. USG abdomen has sensitivity of 75% for pancreatic tumors. Dual-phase helical CT scan allows multiphase imaging during a single bolus of contrast administration, and can achieve sensitivities in the range 82-92 % (Figure 1).

Figure 1: CT showing contrast enhanced tumor on the anterior aspect of the pancreas.



MRI is probably the investigation of choice in defining hepatic metastases. Selective arterial calcium stimulation and hepatic venous sampling (ASVS) using calcium as the insulin secretagogue is a powerful tool for the preoperative localization of occult insulinomas and can also help distinguish the rare forms of noninsulinoma- pancreatogenous-hyperinsulinemia (NIPHS)[3.11,12,13]. Endoscopic ultrasound (EUS) allows the positioning of a high frequency (7.5-10

MHz) transducer in close proximity to the pancreas. Using this approach lesions as small as 5 mm as well as tumours located in the bowel can be detected with a sensitivity of 93% and a specificity of 95% respectively in localization of intra-pancreatic lesions. Intra operative ultrasound (IOUS) also allows direct examination of the pancreas using high resolution 7.5-10 MHz transducers. The combination of IOUS and surgical palpation has led to 97% cure rates in patients with benign insulinomas[3,14]. Preoperative endoscopic ultrasound with fine needle tattooing combined with intraoperative ultrasound can localize the 100% of insulinomas[15].

Treatment of insulinoma is surgery and in most of the cases is curative.. Surgical enucleation is safe and effective. Medical treatment like dizoxide, octreotide are generally used in patients awating surgery, in- operable tumors, or recurrance after surgery if reoperation is not possible [2,3,16].

In these cases of ours, both the patients had typical features of insulinoma and both were non diabetic, healthy with no associated co- morbidities and had been symptomatic for average 3 years before diagnosis, and were in 4th and 5th decade of their lives which is the usual age of presentation. Both had typical episodes of hypoglycemia precipitated in fasting state and excessive exertion.

Despite demonstration of hypoglycemia on previous checkups, this observation was ignored and was wrongly treated as seizures and psychiatry illness. Both the patients presented to us with severe hypoglycemic episode , diagnosis established with demonstration of the whipples triad.. and endogenous hyperinsulinemia . USG abdomen did not reveal any lesion in pancreas but dual phase CT abdomen in both the cases revealed solitary adenomas less than 2 cm diameter. Work up for MEN 1 syndrome was negative. Both were successfully surgically treated with no subsequent episodes of hypoglycaemia reported on follow up. We demonstrated endogenous hyperinsulinemia and could localise the tumor in pancreas. Tumors were solitary approx 2cm in size with no malignant tendency. Both the patients got completely cured with surgical treatment with recurrence.

CONCLUSION

Insulinoma though rare entity is an important cause of hypogycemia. Because of its elusive and deceptive nature,

insulinoma can pose a diagnostic challenge even to an experienced clinician. A high index of suspicion and appropriate laboratory testing demonstrating the presence of inappropriately elevated insulin in the presence of documented hypoglycaemia is the key to successful diagnosis. This may be important as all manifestations of the disease and future complications can be avoided by surgical excision in these patients, which is ultimately curative.

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