Insulinoma : Case Report and Review of Diagnostic and Treatment Modalities

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Abstract

Insulinomas account for 60% of islet cell tumours (ICT) and are typically hypervascular, solitary small tumours, 90% of which measure less than 2cm and 30% measuring less than 1cm in diameter. Approximately 10% are multiple, 10% are malignant and 4-7% are associated with MEN I; these tumours are usually multiple and can be malignant in up to 25%. The tumour is characterized by endogenous hypersecretion of insulin and the subsequent development of symptoms of neuroglycopenia and symptoms resulting from the catecholaminergic response, which may not always be present. Early localisation of the disease is essential to prevent lethal hypoglycaemia. We report a case of insulinoma in a 27 year old male and review of diagnostic modalities to localise the tumour and open v/s laparoscopic enucleation of the tumour.

Introduction

Pancreatic endocrine tumours are rare lesions, with a reported incidence of four cases per 1 million patient-yr.¹ Of these lesions, insulinomas are the most common. The majority of patients diagnosed with an insulinoma are between 30 and 60 yr of age, with women accounting for 59%.² ³ Most insulinomas are sporadic in origin. In two series, 7.6% and 12% of patients with insulinoma had multiple endocrine neoplasia type I syndrome.⁴ Insulinomas are more likely to be multiple in patients with multiple endocrine neoplasia type I.⁴ Almost all insulinomas are located within the pancreas, even though aberrant cases have been described in the duodenum, ileum, lung and cervix.

Patients with insulinoma have symptoms of hypoglycemia resulting from neuroglycopenia and increased catecholamine release.⁵ Surgical excision is the treatment of choice and is curative in most cases. Open or laparoscopic surgery has always remained the topic of debate, depends on the size of the lesion, metastasis and experience of the surgeon. Diagnosis of this pathology relies on clinical features along with laboratory tests and imaging investigations to aid in localisation.

Case Report

A 27 years old male patient, carpenter at building site in uK, had history of episodes of light headedness associated with diaphoresis, palpitation, tremulousness, feeling of impending doom in past, off and on for last 3 years, which were relieved with eating something or taking glucose water orally. As per patient’s information most episodes were in the evening between 1 to 5 pm, and were associated with prolonged fasting and over exertion. Many a times he was carried to the hospital and found to have low blood sugar levels, was treated with intravenous or oral glucose and resolution of symptoms within few minutes. Six months before, he had history of sudden loss of consciousness which lasted for almost 45 minutes before his wife reached to home and patient was carried to a nearby hospital in UK. In emergency room patient was found to have very low sugar, so was given intravenous dextrose and he became conscious after few minutes. As patient was a resident of UK, was investigated for the same there. For further evaluation and management patient was advised hospitalization, but as he was in a queue, he came to India for further work up, but he did not carry any investigations with him. He denied having seizures and diabetes but he noticed increased appetite over the past few years. He had no family history of diabetes, thyroid or pituitary disease. He had never smoked cigarettes or consumed alcohol. There were no prescription medications at the time of his evaluation.

For further evaluation he was advised hospitalization. His physical examination revealed a well-nourished male with weight 73 kg, height 171.0 C.M. BMI 24.0. On the basis of history, keeping insulinoma a possibility; patient was subjected to laboratory investigations for which he was hospitalized and was allowed to take water only with strict monitoring of blood sugar frequently. After fasting, patient developed symptoms of hypoglycemia. At that time on examination his pulse was 120 per minute, blood pressure 150/90 mmHg, respiratory rate was 20 per minute, his abdomen was soft and non-tender with no palpable masses or organomegaly and on central nervous system examination patient was drowsy, arousable with deep pain stimuli with localization of pain, was not following verbal commands, deep tendon reflexes were normal with plantars extensor and pupils mid-dilated. At the same time laboratory investigation were sent. Blood sample taken at the time of hypoglycaemic episode showed low plasma glucose of 49.9 mg/dl, elevated insulin of 94.8 μU/l (normal range, 1.7 - 31 μU/l), elevated C-peptide level of 10.6 ng/ml (normal range 0.9-4 ng/ml), low human growth hormone level of < 0.05 ng/ml(normal range 1 to 5 ng/ml). He was immediately given intravenous glucose and patient became conscious within few minutes.

His serum cortisol level and ACTH levels were normal suggesting intact pituitary adrenal axis. Thyroid function tests were within normal range. Urine for sulfonylurea screen was negative. In view of the clinical picture and laboratory data, the clinical impression was that of an insulinoma. Abdominal ultrasound (US) was normal. A computed tomography of the abdomen and pelvis (Figure 1) with contrast using pancreas...
protocol demonstrated a well-defined hypervascular lesion involving uncinate process of pancreas measuring about 1.3 x 2.2 x 2.1 cm in size with rest normal pancreas. A small hemangima in segment IV of liver was seen. There were no pathological intraabdominal lymph nodes seen.

The patient underwent laparoscopic enucleation of the pancreatic mass 2x2 cm in size. Immediately after removal of the mass, his glucose level increased to 128 mg/dl. Post-operative glucose levels were consistently greater than 100 mg/dl and he experienced no further hypoglycaemic episodes.

Histopathological evaluation revealed a neoplasm composed of nests of cells separated by well vascularized thin fibrous stroma. Neoplastic cell had round, moderately anisomorphic nuclei with small nucleoli and eosinophilic granular cytoplasm. Tumour was partially encapsulated. This was consistent with endocrine neoplasm- insulinoma of pancreas.

The patient was discharged in good health with proper glucose level within 3 day.

**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, including pancreatic tumours that secrete insulin 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. Signs and symptoms of hypoglycaemia are diaphoresis, warmth, hunger, weakness, tingling sensations, paraesthesia, difficulty in thinking, confusion, shaking, tremulousness, tiredness, drowsiness, palpitations, tachycardia, faintness, dizziness, nervousness, anxiety, difficulty in speaking, blurred vision, stupor or coma.

The diagnosis of insulinoma is suggested by endogenous hyperinsulinaemia in the presence of hypoglycaemia and reversal of the symptoms by administration of glucose (Whipple’s triad). Insulinomas are uncommon- the yearly incidence is estimated to be 1 in 2,50,000. Insulinomas account for 60% of islet cell tumours (ICT) and are typically hypervascular, solitary small tumours, 90% of which measure less than 2cm and 30% measuring less than 1cm in diameter. Approximately 10% are multiple, 10% are malignant and 4-7% are associated with MEN I; these tumours are usually multiple and can be malignant in up to 25%. Almost all insulinomas are located within the pancreas, even though aberrant cases have been described in the duodenum, ileum, lung and cervix. The tumour is characterized by hypersecretion of insulin and the subsequent development of symptoms of neuroglycopenia and symptoms resulting from the catecholaminergic response, which may not always be present.

In patients with insulinoma, there is continued secretion of insulin despite a lower glucose level. Insulin is synthesised as a single-chain precursor proinsulin – which is cleaved into a C-peptide and insulin, both of which are secreted in equimolar concentrations. 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. Hypoglycaemia induced by sulphonylurea may have an identical presentation like an insulinoma; a negative screening for sulphonylurea is required to confirm the diagnosis. Our patient was fitting into all the above mentioned criteria.

Once a clinical and biochemical diagnosis is established, the imaging modalities are used for localisation of tumour. Recently, several prospective studies have investigated the relative utility of currently available techniques, and helped to establish a diagnostic work-up on evidence-based information. 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. 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. EUS detected all tumours visualized by any other conventional technique questioning the necessity for other imaging modalities. 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. In addition, besides facilitating surgical resection, IOUS can help define the appropriate plane of resection by identifying multiple small tumours, in patients with MEN 1.

The majority of ICT are isodense on unenhanced CT and will not be seen without intravenous contrast enhancement. Dual-face helical CT scan allows multiphase imaging during a single bolus of contrast administration, and can achieve sensitivities in the range 82-92%. A comparative study showed that the sensitivity of T1-weighted MR imaging is equivalent to delayed Portal Venous Phase (PVP) dynamic CT. Due to the relative rarity of islet cell tumours, it remains difficult to define the best imaging technique, although MRI is probably the investigation of choice in defining hepatic metastases. MRI is considered the most sensitive technique for demonstrating liver and bone metastases in patients with gastroenteropancreatic (GEP) tumours and is recommended for precise monitoring of response to therapy. In cases of small insulinomas not detected with the previously mentioned imaging modalities, invasive procedures may still be necessary to achieve pre-operative localization. Sensitivities ranging between 77 and 100% have been described for trans-hepatic portal venous sampling (TPVS), but this technique is associated with considerable morbidity. 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 non-insulinoma-pancreatogenous-hyperinsulinemia (NIPH). In a recent series of 11 patients a sensitivity of 100% was obtained with this technique, which may also identify rare extra-pancreatic insulin-secreting Neuroendocrine Tumours (NETs), mainly of the liver. Positron emission tomography (PET) using 18F-FDG and 68Ga-DOTATOC, can also be considered.
hydroxytryptamine (HTP), due to selective uptake in tumour tissue compared to surrounding tissue, produces very good tumour visibility and it can be used for the examination of both the thorax and abdomen. However, lack of general availability and high cost limits its use. Intra-operative nuclear imaging can be used to help define the exact location of a biochemically proven GEP and aid in its complete resection.

Conventional imaging studies such as ultrasonography, CT, and MRI fail to reveal the majority of insulinomas. However they have a role in the evaluation of malignant insulinomas and in the detection of metastases. Portal vein sampling and intra-arterial stimulation of insulin secretion with calcium makes it possible to detect almost all insulinomas but they are invasive and complicated techniques. IOUS alone identifies approximately 95% of tumours but necessitates experience for the surgeon or assistance by a radiologist. Laparoscopic ultrasound as an integral part of laparoscopic procedure has also been suggested in the management of these patients. However inability to localize the tumour during laparoscopic approach and conversion rate has been reported as high as 30% in a recent multicentre study.

Preoperative endoscopic ultrasound with fine needle tattooing combined with intraoperative ultrasound can localize the 100% of insulinomas. The technique was first advocated by Gress et al. It needs experienced endoscopist and surgeon familiar with pancreatic surgery. The overall sensitivity and accuracy of EUS is over 90% for insulinomas and EUS-FNT helps even more in localizing the site of the lesion. Our case supports the use of EUS and EUS-FNT as a primary modality in the evaluation, localization and treatment of patients with insulinomas. Nevertheless, CT and MRI scan are still useful in the assessment of malignancy and identification of adjacent lesions.

Laparoscopic enucleation is safe and effective. If the lesion seen on CT is well defined, it can be removed laparoscopically. Endoscopic ultrasonography is useful for identifying lesions in patients whose CT scans are nondiagnostic. Some previous studies have shown that pancreatic fistulas were common, but they resolved spontaneously and produced little morbidity. Laparoscopic enucleation resulted in a short hospitalization and rapid recovery for most patients. Our patient also underwent laparoscopic enucleation, had no post operative complications and he was discharged from the hospital on 3rd post op day.

![A computed tomography of the Abdomen and pelvis with contrast using pancreas protocol demonstrated a well-defined hypervascular lesion involving uncinate process of pancreas measuring about 1.3 x 2.2 x 2.1 cm in size with rest normal pancreas. A small hemangioma in segment IV of liver was seen. No pathological intraabdominal lymphnodes seen.](image)
References


