Diagnostic pitfall in hypoglycemia: Insulinoma in tail of pancreas

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Abstract

Insulinomas, a rare kind of tumors are the most common cause of endogenous hyperinsulinsm with patients presenting with the classical Whipple's triad.

We present a patient with neurohypoglycemic symptoms undergoing neurological/psychiatric evaluation in multiple hospitals. A detailed workup in our hospital revealed a small tumor in the tail of pancreas and enucleation of tumor was successfully performed. After surgery, patient's symptoms were resolved and patient did not report any episodes of hypoglycemia during 3 months follow-up period.

Diagnosis of insulinoma is difficult due to its low incidence and presence of neuroglycopenic symptoms. Patients tend to seek neurology opinion early on and in many cases the diagnosis is delayed due to futile search for neurological or psychiatric illnesses. Hence a multimodal approach including endocrinologist, surgeons, radiologist and pathologist is required.

Keywords: Hypoglycemia; Whipple’s triad; Insulinoma; Tail of pancreas; Enucleation

1. Introduction

Endogenous hyperinsulinism is a rare cause of hypoglycemia wherein insulinomas are the commonest cause of endogenous hyperinsulinism. Insulinomas are rare tumours but are most common amongst pancreatic neuroendocrine tumors with an incidence of 1-32 cases/million persons/year 1 and median age at presentation being 50 years.

Insulinomas are rare pancreatic neuroendocrine tumors of which 90% are benign, solitary, intrapancreatic and small in size (<2cm in diameter) 2. Less than 10% are malignant, multiple or present with MEN-1 syndrome. They are insulin secreting tumors of the pancreas with equal distribution within the head, body and tail of pancreas.

However, the nonspecific neuroglycopenic manifestations make it a diagnostic challenge for medical practitioners. Diagnosis of suspected cases can be easily confirmed by standard endocrine tests but because of nonspecific symptoms, insulinomas are either diagnosed late or misdiagnosed as neurological or psychiatric illness. After biochemical confirmation of hyperinsulinism and preoperative radiological localization, surgical resection is often curative and remains the primary treatment modality for insulinomas.

This review aims to present a case report and summarize the current literature evidence on insulinomas and discuss the importance of inter-disciplinary approach required for early diagnosis and management of insulinomas.

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2. Case Report

A male in his 60s presented with recurrent episodes of sweating, palpitations, tremors, dizziness, and loss of consciousness since 1 year. Patient was evaluated for his symptoms in other hospital before being brought to our Emergency department[ED]. History revealed prior multiple admissions in outside hospitals for similar symptoms with recorded random blood sugar[RBS] levels less than 50 mg/dl during the episodes. On every occasion, intravenous glucose infusion led to resolution of his symptoms. He had no family history of endocrine disease. Patient's attendants also gave history of 2 episodes of dizziness followed by loss of consciousness for which a neurology consultation was sought. Magnetic Resonance Imaging of brain to look for intracranial pathology was normal. Patient reported to our ED with a RBS of 39 mg/dl and he was admitted for further evaluation after initial stabilization. Endocrinology reference was taken and a diagnosis of insulinoma was suspected based on identification of classical Whipple's triad.

Prolonged supervised fasting test to produce symptomatic hypoglycemia revealed raised insulin levels of 6.40 (>3uU/ml), raised C peptide levels of 1.62 (>0.5 nmol/L), and raised pro-insulin levels of 7.3 (>5pmol/L) during hypoglycemia which was indicative of endogenous hyperinsulinism.

Triple phase Contrast Enhanced Computed Tomography[CT] of abdomen revealed well circumscribed, homogenously enhancing lesion measuring approximately 19x18mm in tail of pancreas with enhancement during the arterial phase. There was no evidence of multifocal disease, or lymph node involvement on CT. The lesion was away from main pancreatic duct and splenic vessels for preoperative surgical accessibility.

Hormonal studies including serum cortisol, prolactin, calcium, parathormone levels and thyroid profile were normal. In view of normal hormonal assessment and MRI brain, multiple endocrine neoplasia was eliminated.

Sulfonylurea- induced hypoglycemia was ruled out as patient was not a diabetic. Biochemical sulfonylurea screening could not be performed due to unavailability of the test at our center.

After establishing a diagnosis of insulinoma based on clinical, biochemical and radiological investigations, a decision of surgical resection was made. All preoperative routine investigations (CBC, LFT, RFT, PT/INR, viral markers) and Pre Anesthesia Checkup were done and patient was planned for diagnostic laparoscopy and lap/open surgery. As the tumor was in tail of pancreas, distal pancreatic resection would have led to type 2 diabetes mellitus in patient, so enucleation of tumor was planned. Diagnostic laparoscopy did not reveal any evidence of widespread or metastatic disease. Open surgical exploration was done using Chevron surgical incision. During the surgical procedure, after achieving adequate surgical exposure and mobilization of pancreas, careful bimanual palpation of pancreas revealed a firm and well

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Figure 1 A pre operative CT abdomen Scan showing tumor in tail of pancreas

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circumscribed tumor at the tail of pancreas. A frozen section taken from the mass was suggestive of neuroendocrine tumor.

Following confirmation of tumor, enucleation was successfully performed. Pathological examination revealed an encapsulated mass measuring 25x15mm. Mitotic index was 0-1 per 10 high power fields (HPF) and proliferation index ki-67 was estimated at 1-2%. Morphological features were suggestive neuroendocrine tumor grade 1. Immunohistochemically, tumor cells showed a positive and diffuse staining for synatophysin, chromogranin and CD56. Final diagnosis of a low grade neuroendocrine tumor of pancreas-insulinoma was established.

There were no hypoglycemic episodes in the post operative period and patient was discharged on POD4. The patient remains asymptomatic after 3 months follow up.

![Figure 2 Intra operative images while enucleation being performed](image1)

![Figure 3 Resected specimen](image2)

![Figure 4 Histopathological pictures showing diffuse synaptophysin and chromogranin positivity in tumour cells](image3)

**Final impression**
Well differentiated neuroendocrine pancreatic tumor grade 1

3. Discussion

Insulinoma is the most common pancreatic functioning NET and the most common cause of hypoglycemia related to endogenous hyperinsulinism. The clinical features of hypoglycemia can be divided into neuroglycopenic (most common) due to direct result of CNS glucose deprivation and neurogenic or autonomic manifestations. Neuroglycopenic symptoms include confusion, fatigue, headache, irritational behaviour, seizures and loss of consciousness and neurogenic symptoms include sweating, tremor, anxiety, palpitations, hunger and paresthesias. These symptoms become evident on prolonged fasting, can be precipitated by physical exercise and typically resolve after reversing the hyperglycemia.
These neurological symptoms lead patients to misinterpret their symptoms as part of cardiac, neurological or psychiatric disorder hence delaying the diagnosis or being misdiagnosed.

Around 20% insulinoma cases had been misdiagnosed with a neurologic or psychiatric disorder before insulinoma was recognized\(^1\). In our report, insulinoma diagnosis was delayed for months as symptoms were misattributed to neurological disorder and patient was being investigated and evaluated for neurological illness.

Insulinoma should be suspected in patients in whom Whipple’s triad is documented. Whipple’s triad remains the cornerstone of the screening process and the classical diagnosis of insulinoma depends on satisfying the criteria:

- Hypoglycemia (low plasma glucose concentration<45mg/dl)
- Clinical signs/symptoms consistent with hypoglycemia, and
- Resolution of symptoms when the plasma glucose concentration increases should be documented during initial evaluation.

In our case, despite repeated visits to the emergency room in various hospitals, patient’s symptoms of hypoglycemic episodes were attributed to fasting or exertion. No attempt was made to identify the cause of the hypoglycemia thus delaying the diagnosis. The most reliable test to diagnose insulinoma is supervised 72hr fasting test and at the time of hypoglycemia, measurement of plasma glucose, insulin, c-peptide and pro insulin levels for biochemical diagnosis\(^3\).

In our patient diagnostic hallmark of insulinoma, i.e. Whipple’s triad was met and we used the above biochemical tests to establish the diagnosis. Levels of insulin, c-peptide and pro insulin were elevated in the setting of hypoglycemia.

When endogenous hyperinsulinism hypoglycaemia is present, imaging studies are performed. These may include non invasive techniques for localization of a suspected insulinoma, such as transabdominal ultrasonography, CT and/or MRI and/or PET scans. These imaging studies are successful in identifying 75% of insulinomas.

Insulinomas demonstrate characteristic features when imaged with conventional CT or MRI with reported sensitivity of detection ranging from 33-64% and 40-90% respectively. However, the advent of multidetector helical CT has enabled detection of 94.4% of pancreatic insulinomas. Consequently, CT scan is currently accepted as first line and MRI as second line investigation for localization of insulinomas in practice\(^1\).

In our context we used triple phase CECT abdomen for the diagnosis which revealed enhancing solid tumor in tail of pancreas suggestive of pancreatic NET.

Gallium Ga-68 DOTATATE PET/CT, a somatostatin receptor based imaging modality is an option when conventional imaging studies do not identify an insulinoma or to rule out ectopic insulin secretion.

We did not do a DOTA scan in our patient as tumor was already picked up on the CECT abdomen and due to added cost to the patient and financial burden.

Invasive diagnostic modalities such as EUS and ASVS have been shown to be highly accurate and superior to non invasive techniques in preoperative localization with reported detection rates of 86-92.3% and 94-100% respectively. EUS can detect small tumor of even 5mm and allow performing EUS-guided FNA but it is largely operator dependent. EUS is the test of choice in case of inconclusive results in aforementioned first line imaging tests.

In our institution we use EUS when the tumor is not detected with the above mentioned non-invasive imaging modalities and EUS guided FNA in our context was difficult as tumor being inaccessible located in the tail of pancreas. The addition of ASVS helps identifying a tumor by verifying hormonal function but this is not commonly performed for detection of insulinomas at our centre.

Intraoperative bimanual palpation combined with IOUS in the hands of trained IOUS surgeons is most effective method to precisely detect upto 93% of tumors but requires complete mobilization of the pancreas. It is utilized when tumor remains undetected as in occult or non-detectable insulinomas on imaging modalities after exclusion of other conditions associated with fasting hypoglycemia.

Surgical resection can be curative for insulinomas and the patient should be operated after diagnosis of insulinoma is confirmed along with preoperative topographic localization. Insulinomas come to attention because of hypoglycemia.
rather than mass effects. 99% tumors are within the substance of pancreas and tumors are usually small <2cm in 90% of cases.

The choice of surgical procedure depends on the size and location of mass. Tumor enucleation is the procedure of choice in management of insulinomas located way from the MPD and major vessels with advantage of preserving pancreatic parenchyma, thereby reducing the risk of late endocrine/exocrine insufficiency. The lesions are typically firm, encapsulated, reddish-brown with a clear plane of dissection between the tumor and surrounding pancreas. Recent guidelines suggest that enucleation is enough in well circumscribed lesion with clear preoperative and intraoperative localization, with tumor located near or at the pancreatic surface. Despite advances in laparoscopic surgery, insulinoma open surgery is the most widely accepted method of resection. Approximately 17-25% of laparoscopic procedures are converted to open due to technical operable difficulties, homeostasis, presence of intraabdominal adhesion and proximity to splenic vessels.

Our patient underwent successful tumor enucleation using open surgical approach. The mass was easily identified with bimanual palpation at the tail of pancreatic parenchyma after mobilization of the pancreas. Large tumors (invading or in close proximity with pancreatic duct or major vessels), high suspicion of malignancy (hard infiltrating tumor), PD dilatation or metastasis indicate the need of distal pancreatectomy (with or without splenectomy), Whipple's procedure (PPPD) as the procedure of choice instead of enucleation.

Lymphadenectomy is not included as routine in patients with benign neoplasm, but is mandatory in context of malignant tumors and extensive pancreatic resections.

Histopathologically, insulinomas are epithelial neoplasms which are classified under pancreatic neuroendocrine tumors into different grades based on immunohistochemistry. Insulinomas express strong and diffuse positivity for neuroendocrine markers such as synaptophysin and chromogranin. Mitotic rate and Ki-67 proliferation index are particularly helpful to distinguish well differentiated from poorly differentiated tumors.

Conversely, benign and malignant tumors are difficult to differentiate on HPE and diagnosis of malignant insulinoma is confirmed by presence of metastatic disease. Most patients with malignant disease have liver or lymph node metastasis at presentation.

Medical treatment with alpha-glucosidase inhibitors (acarbose, miglitol, calcium channel blockers (verapamil), Diazoxide or somatostatin analogue (octreotide) can be used if resection is not possible due to metastatic tumours, persistent symptoms after resection or as a measure to treat and prevent hypoglycemia for patients awaiting or refusing surgery. Moreover, other recent multimodal therapy such as selective or chemoembolization, Radiofrequency ablation can prolong the survival of malignant insulinomas in patients who failed the usual medical and surgical treatments.

Chemotherapy has been used in insulinomas with varying degrees of success and limited experience. The traditional regimen of choice with streptozocin and doxorubicin is used for metastatic islet cell tumors. Uncertainty about its efficacy and systemic toxicity of this chemoregimen has prevented its widespread acceptance as standard first line therapy.

There are no evidence based guidelines for followup after resection of a benign insulinomas however malignant insulinomas should be followed up 3-12 months post resection with clinical history and imaging studies if needed.

4. Conclusion

The hypoglycemic manifestations of insulinoma present with variable symptoms thereby resulting in invariably delayed diagnosis. All patients with recurrent episodes of hypoglycemia should be evaluated biochemically for endogenous hyperinsulinism.

A low threshold for early identification of classical Whipple’s triad is needed at the level of primary care physician/ER team to direct timely medical diagnosis and surgical treatment for insulinoma. This can save the patient from inconvenience and financial burden of multiple hospital visits, delayed diagnosis and misdirected futile investigations.
A multidisciplinary approach involving physician, endocrinologist, radiologist and surgeon is essential for optimal outcomes. Surgery with enucleation is the standard of care for small, localized and peripheral pancreatic insulinomas and is curative in most patients. Follow up is essential to identify recurrence of symptoms post resection. Hence patients should be educated about need and benefits of post-surgery surveillance.

Compliance with ethical standards

Disclosure of conflict of interest
The authors declare no conflict of interests.

Statement of ethical approval
The present case report does not contain any studies performed on human subjects by any of the authors.

Statement of informed consent
Informed consent was obtained from the patient involved in this case report.

References


