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CASE REPORT

# Insulinoma: A rare cause of hypoglycemia in a young female

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Insulinoma is an exceedingly uncommon pancreatic islet cell neuroendocrine tumor. The estimated incidence is approximately four cases per million individuals per year and accounts for 60% of islets cell tumors. It causes glycopenic symptoms which includes headache, feeling irritable, confused, seizure or coma and leads to catecholamine excess which includes rapid heartbeat, sweating, palpitations and feelings of hunger. Early detection of the tumor prevents recurrent episodes of lethal hypoglycemia.

Keywords: *insulinoma*; *lethal hypoglycemia*; *Pancreas tumor*; *neuroendocrine tumor*; *islet cell tumor*

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Our patient is a 22-year-old female college student whose only past medical history includes 2 years of recurrent hypoglycemia episodes. She does not take any prescription medications or over-the-counter supplements. Her social history includes drinking one to two beers on the weekends. She lives alone, works at a local restaurant, and none of her family members have a history of diabetes mellitus or any cancer.

Her first episode of hypoglycemia occurred in October 2012. She was found in her car, after she had run off the road and was stopped by a bush. Her air bags did not deploy, and emergency medical services personnel broke open her car window to reach her. She was awake but unable to follow commands. She was found to have stable vital signs with a heart rate of 120 beats/min and blood glucose level of 35 mg/dl which increased with intravenous dextrose and glucagon injection. She attributed her symptoms to fasting overnight and skipping breakfast in the morning. She refused hospitalization at that time.

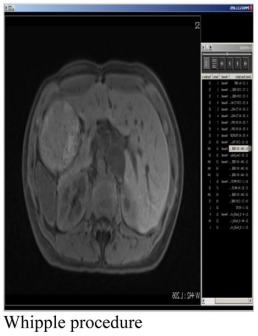
She subsequently experienced further hypoglycemic events in January 2013 during a volleyball tournament, in April 2013 while at a wedding, and in May 2013 while on a cruise. Her last episode resulted in a generalized tonic-clonic seizure. All of the episodes resulted in the rescue squad being called, and she was found to be hypoglycemic each time. All resulted in recovery with intravenous dextrose and glucagon injection.

She was eventually admitted the hospital for a 72-h fasting blood glucose evaluation. During the first 12 h, her blood glucose dropped to 35 mg/dl, with associated drowsiness and confusion and responded to IV dextrose. Laboratory serum studies demonstrated increased proinsulin 73.6 pmol/L, insulin 23 uIU/ml, C peptide level 1.93 ng/ml, and beta hydroxybutyrate 0.0 mmol/L ($<0.6$ mmol/L). Her serum sulfonylurea screen was negative, and insulin antibody titer was normal at 0.3 U/ml.

She had an abdominal MRI which revealed a $1.7 \times 1.7$ cm arterial enhancing mass in the pancreatic head without any local invasion or metastases.

She was referred to a tertiary care center and had a Whipple procedure, was performed without complication. The pathology report showed well differentiated insulinoma with no local or distant metastases. She remained asymptomatic with no recurrent symptoms for the next 6 months and her repeat MRI of the abdomen was negative for residual tumor.

Pancreatic tumor (head of the pancreas)



Whipple procedure





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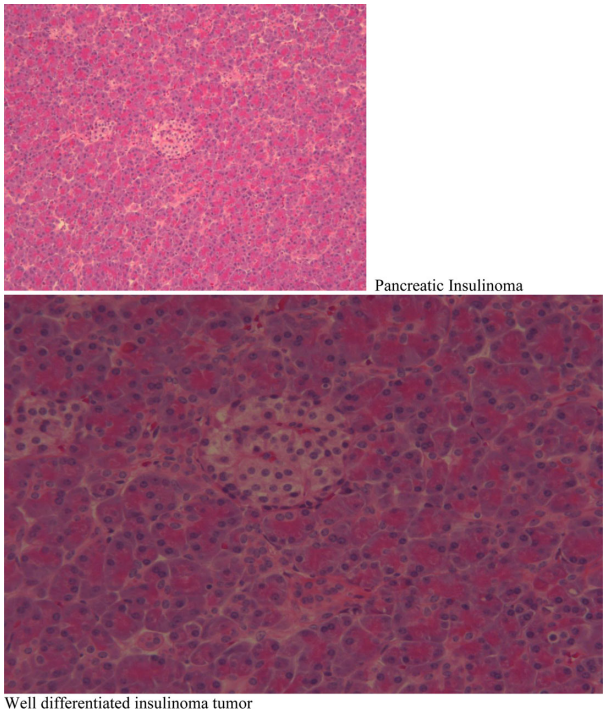

Pancreatic Insulinoma

Well differentiated insulinoma tumor

## Discussion

Insulinoma is an uncommon neuroendocrine pancreatic tumor. The incidence of insulinoma peaks at 30–60 years of age and is more frequent in women (1, 2). Its estimated incidence is approximately four cases per million individuals per year (1). Insulinoma are generally small ( $<2$ cm) and usually not multiple (90%). Only 5–15% are malignant, and they almost invariably occur only in the pancreas, distributed equally in the pancreatic head, body, and tail (3).

The most common clinical symptoms are due to the effect of hypoglycemia on the central nervous system (glycopenic symptoms) and include confusion, headache, disorientation, seizure (4), visual difficulties, irrational behavior, and even coma (5). In addition, most patients have symptoms due to excess catecholamine release secondary to the hypoglycemia, including sweating, tremor, and palpitations. Characteristically, these attacks are associated with fasting.

The diagnosis of insulinoma requires the demonstration of an elevated plasma insulin level at the time of hypoglycemia. The most reliable test to diagnose insulinoma is a 72 hour fasting serum glucose, C-peptide, proinsulin, and insulin measurements every 4–8 h. If at any point the patient becomes symptomatic or glucose levels are persistently below $<2.2$ mmol/L (40 mg/dl), the test should be terminated and repeat samples for the above studies should be obtained before glucose is given. Generally 70–80% of patients will develop hypoglycemia during the first 24 h and 98% by 48 h (3).

Surreptitious use of insulin or hypoglycemic agents may be difficult to distinguish from insulinomas. The combination of proinsulin levels (normal in exogenous insulin/hypoglycemic agent users), C-peptide levels (low in exogenous insulin users), antibodies to insulin (positive in exogenous insulin users), and measurement of sulfonylurea levels in serum or plasma will allow the correct diagnosis to be made (3).

Unlike most endocrine pancreatic tumors, the majority (90%) of insulinoma are benign and solitary, and only 10% are malignant. They are typically cured by simple enucleation. However, tumors located close to the main pancreatic duct and large ( $>2$ cm) tumors may require a distal pancreatectomy or pancreaticoduodenectomy (6). Surgical resection is the most definitive and curative treatment for insulinoma.

Sometimes, the lesions are unresectable or metastasis to the liver or regional lymph node. In such cases, the treatment approach is variable depending on the extent of metastasis and functional status of the patient.

Medical therapy may be considered for the non surgical patient and approach to control hypoglycemia events by decreasing insulin production or antagonizing insulin effect at receptor level. Diazoxide is the most commonly used oral medication to control hypoglycemia but it causes side effects includes edema and excessive hair growth (7).

Octreotide and Lanreotide may be used to control hypoglycemia. These agents also offer some tumor regression but are not as effective as surgery (8, 9).

Alternatives to medical therapy include, external beam radio therapy can produce high rates of symptom palliation and freedom from local progression in patients who are not candidates for surgical resection (10, 11). Surgical resection of tumor should be considered in limited number of hepatic metastases without excessive local tumor burden and which have acceptable liver function test (12).

In limited case reports, hepatic artery selective chemoembolization, which predominate supplies cancer hepatocytes, is frequently applied as a palliative technique in patients with symptomatic hepatic metastases who are not candidates for surgical resection (13, 14). Alternative approaches include radiofrequency ablation and cryoablation and are applicable techniques for smaller lesions, but their long-term efficacy remains uncertain (15).

Limited randomized controlled trials, and rare incidence of disease with little literature data available, have limited systemic chemotherapy approach for metastatic disease, but well-differentiated pancreatic tumors do respond to cytotoxic chemotherapy including streptozotocin and doxorubicin, and have a combined biochemical and radiographic response rate of 69% and a medical survival of 2.2 years (16).



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There are no evidence-based guidelines for follow-up after resection of a malignant insulinoma but they generally include complete history and physical examinations every 3–6 months and imaging study for recurrence of disease.

## Conclusion

Insulinoma is an exceedingly uncommon pancreatic islet cell neuroendocrine tumor. The estimated incidence is approximately four cases per million individuals per year. It should be one of the working diagnoses in young patients with multiple events of hypoglycemia. Insulinomas are generally 90% benign tumors with excellent surgical result and have good long term prognosis.

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