ISSN: 2584-0355
DOI: doi.org/10.51219/MCCRJ/Gabriela-Mintegui/431

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Medical & Clinical Case Reports Journal

https://urfpublishers.com/journal/case-reports

Vol: 4 & Iss: 1

Case Report

Malignant Insulinoma: Case Report and Literature Review

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Citation: Cabral S, Casella C, Mintegui G. Malignant Insulinoma: Case Report and Literature Review. *Medi Clin Case Rep J* 2026;4(1):1564-1568. DOI: doi.org/10.51219/MCCRJ/Gabriela-Mintegui/431

Received: 07 January, 2026; **Accepted:** 12 January, 2026; **Published:** 14 January, 2026

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ABSTRACT

Summary

Insulinoma is a neuroendocrine tumor of the pancreas capable of secreting insulin. They are rare and the incidence varies according to the center considered. Fasting hypoglycemia in a non-diabetic patient (blood glucose below 55 mg/dl) is the most common clinical manifestation of insulinoma and the presence of neuroglycopenic symptoms that may be preceded by autonomic symptoms. The diagnosis of insulinoma requires inappropriately high levels of insulin and C-peptide, associated with hypoglycemia. After the biochemical diagnosis, the tumor must be located by imaging techniques such as ultrasound and computed tomography of the abdomen. Malignant tumors have little or no cellular pleomorphism, hyperchromasia or high mitotic activity, tend to have a worse prognosis and the management of hypoglycemia, as well as the resolution of associated metastases, is a challenge. The benefit of primary tumor resection in patients with metastatic pancreatic neuroendocrine tumors is also controversial.

Keywords: Hypoglycemia; Insulinoma; Neuroendocrine tumors

Introduction

Insulinoma has an incidence of approximately 4 cases per million inhabitants per year (1-3) and is frequently benign, single, sporadic and less than 20 mm[1-5]. Between 2-7% present as part of a Multiple Endocrine Neoplasia type 1 (MEN1) syndrome and up to 6% may present liver or lymph node metastases (malignant insulinoma)[1-5].

In insulinoma, a median age at diagnosis of 56 ± 18 years has been described and no differences between genders have been observed[6].

Its usual clinical presentation consists of the so-called Whipple Triad (characterized by the presence of symptoms: tremor, sweating, tachycardia; low blood glucose levels and relief of these symptoms by ingesting carbohydrates)[5].

Hypoglycaemia is mainly due to reduced hepatic glucose production, rather than increased glucose utilization[7].

There are neuroglycopenic symptoms such as: confusion, visual changes and unusual behaviour and then sympathetic-adrenal symptoms: palpitations, diaphoresis and tremors. In addition, there could be hyperphagia, which can determine weight gain in these patients.

Diagnosis of insulinoma requires the demonstration of excessively high plasma insulin concentrations during an episode of spontaneous or provoked hypoglycaemia.

Once the laboratory diagnosis has been made, the location of the tumour is required and transabdominal ultrasound and computed tomography are preferred. When the tumour is not located by initial imaging studies, additional options include other non-invasive or invasive tests such as endoscopic ultrasound (endoscopic ultrasound). This is a highly sensitive and specific procedure for the localization of pancreatic endocrine tumours[8]. Somatostatin receptor scintigraphy, on the other hand, is proposed for the detection of insulinomas, when endoscopic ultrasound is negative[9].

Other non-invasive imaging tests include magnetic resonance imaging and fluorine-18-L-dihydroxyphenylalanine positron emission tomography (18F-DOPA PET) (10). Ga-68 gallium PET/CT (a somatostatin receptor-based imaging modality) is an option when conventional imaging studies do not identify an insulinoma. It is capable of identifying most of these tumours and can be considered as a complementary imaging study when all imaging studies are negative and when surgical treatment is planned[11].

The World Health Organization established a classification of malignant gastroenteropancreatic neuroendocrine tumours based on a scheme of criteria such as tumour size < 2 cm versus > 2 cm and presence of metastasis; grade (mitotic rate, perineural and lymph vascular invasion, proliferative index Ki-67)[12].

Another classification scheme estimates malignant potential using accurate prognostic information by combining tumour size and metastases with simple classification information based on necrosis and mitotic rate[13].

Treatment of sporadic insulinomas is surgical, but when it is more than one lesion, it is debatable because it requires very extensive procedures with endocrine and exocrine pancreatic functional loss.

The liver and regional lymph nodes are the most common sites of metastatic disease. In these cases, surgical treatment, hepatic artery embolization, radiofrequency, cryoablation or even systemic therapy are considered[14].

Medical treatment to control hypoglycaemia is necessary in patients who are not subject to surgery or in those who have unresectable metastatic disease or to control recurrent hypoglycaemia while waiting for surgery[14].

Diazoxide is used in the first line, but octreotide or lanreotide because they are somatostatin analogues and as other options verapamil or phenytoin can be used.

If postoperative remission is achieved, the probability of recurrence of insulinoma is low (<10%), but survival is worse in older patients and in those with metastatic disease[15].

Clinical Case

A 33-year-old man with a history of psychiatric pathology treated with risperidone since childhood. In the previous three years, he presented multiple episodes of symptomatic hypoglycaemia that required hospital admission and management with continuous infusion of glucose serum, with blood glucose values that reached 35 mg/dl, seizures and loss of consciousness, which require management in intensive care. During the evaluation, a computed tomography of the abdomen was requested, which showed 2 pancreatic lesions, one in the body of 28 mm and another in the uncinate process of 42 mm. Additionally, multiple focal lesions were found in the liver, the largest of which was 32 mm **(Figure 1)**. Likewise, venous glycemia of 37 mg/dl, insulin of 137 (normal range 2 to 12 µU/mL) and increased C-peptide of 8.27 (normal range 1.1 to 4.4 ng/ml) were found, which allowed a diagnosis of malignant insulinoma with liver metastases. A PET-CT scan with 18F-NOTATOC confirmed that pancreatic and hepatic lesions expressed somatostatin receptors **(Figure 2a and 2b)**.

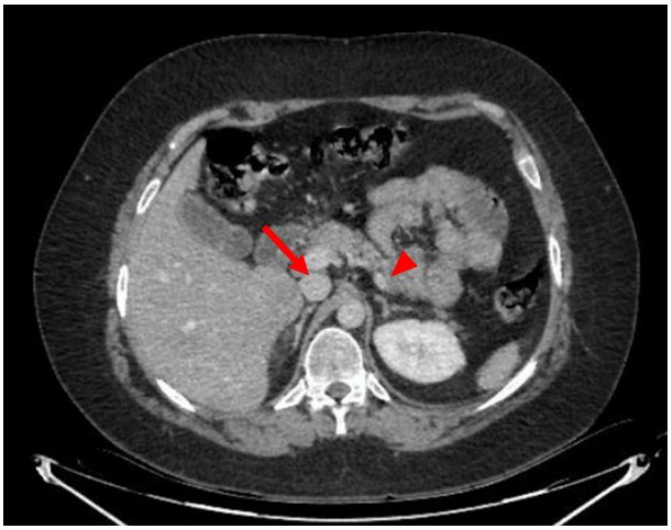

Figure 1: Axial computed tomography scan. Insulinoma is observed on the right in the uncinate process (arrow) and on the left (arrowhead).

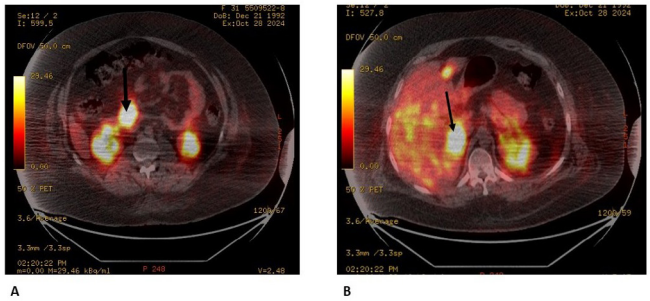

Figure 2: PET with 18F-NOTA-OCT

A: insulinoma uptake is observed (arrow);

B: uptake of multiple liver metastases and the largest one (image on the right)

Since the disease was in an advanced stage, surgical intervention was ruled out and other treatments were chosen in parallel. In May 2022, two trans arterial embolization's were performed in which the lesion in the head of the pancreas and a couple of liver lesions were eliminated, although the lesion in the body of the pancreas and other hepatic lesions persisted. As

pharmacological treatment (May-June 2022), immediate-release octreotide (400 mcg c/8 hours) and diazoxide (200 mcg c/8hs) were initiated.

Additionally, a dose of lutetium was administered, with a good therapeutic response achieving glycemia, between 100-200 mg/dl without the need for glucose serum and significant reductions in insulinemia values: 12.8 µU/mL and C-peptide: 2.80 ng/ml. Under these conditions, he is discharged, with evolutionary control. During follow-up, he received 3 additional doses of Lutetium: (August 2022, November 2022 and January 2023). However, she did not maintain follow-up with endocrinology and received diazoxide only for the first month, opting to maintain only extended-release octreotide for 28 days. In October 2024 he was admitted to hospital for episodes of symptomatic severe hypoglycaemia of up to 20 mg/dl. It was necessary to use a continuous infusion pump of 30% glucose serum for stabilization. Given the persistence of hypoglycaemia, the use of glucocorticoids was attempted to promote hepatic gluconeogenesis and reduce hyperinsulinemia. However, this treatment was not effective and the infusion of glucose serum was maintained. A new 18F-NOTE-OCT PET scan was performed, which showed the same hyper uptake lesions in the pancreas and liver, but larger than in the previous study.

In addition, he presented intense bone pain that limited his ambulation, so a pelvic MRI was requested that confirmed osteonecrosis of both femur heads.

Biochemical analyses showed calcemia of 10.5 mg/dL (normal range of 8.3 - 10.3 mg/dL), PTH of 243 pg/mL (normal range 15 - 65 pg/mL), with vitamin D < 3 ng/mL (normal range 30-120 ng/mL), phosphate, azoemia and normal blood creatinine. Urine/24-hour calciuria was also normal. With the approach of primary hyperparathyroidism, a neck ultrasound was requested, which showed a well-defined hypoechogenic solid nodular lesion, without vascularization of 9 x 7 x 7 mm, topographer in the left lower posterior thyroid sector. Parathyroid scintigraphy could not be performed.

During hospitalization, an attempt was made to embolize the lesions, but it was not possible to locate the nutritious arteries of the tumours. Lutetium was requested, but the tracer radio was not accessed. Despite the glucose serum and diazoxide, the patient presented seizures that culminated in his death.

Discussion

The presence of Whipple's triad, as in this case, supports the presence of pathological hypoglycaemia. Adequate questioning and physical examination, with the complementary laboratory, determine the aetiology of hypoglycaemia in a non-diabetic patient. In people without underlying diseases, who do not take drugs that cause hypoglycaemia like this patient, the most likely aetiologies of hypoglycaemia are endogenous hyperinsulinism or factitious hypoglycaemia[16].

The onset of hypoglycaemic symptoms usually occurs when blood glucose levels drop below 55 mg/dL, although the specific threshold varies between individuals and over time. The counterregulatory response (such as the release of glucagon and epinephrine) may appear with glycaemic levels approximately 10 mg/dl higher, before the onset of hypoglycaemic symptoms. In addition, glycaemic thresholds for these counterregulatory responses may be higher in patients with insulinoma[17].

Although fasting hypoglycaemia is the most common presentation of insulinoma[18], postprandial hypoglycaemia may be a concurrent or even the only manifestation of hypoglycaemia in some patients, although the proportion is low[19].

Up to 20% of patients with insulinoma receive a misdiagnosis of a neurological or psychiatric disorder before the insulinoma is recognized[20,21].

We are left with the doubt in this case, treated for psychiatric pathology with episodes suggestive of hypoglycaemia of three years of evolution, which were not previously studied if they were not interpreted as part of his psychiatric illness of years of evolution and therefore the diagnosis of hypoglycaemia is delayed.

There is a case series report with insulinoma, which showed that approximately 77% presented autonomic symptoms and 96% neuroglycopenic symptoms; ≥80% presented confusion or abnormal behaviour, 50% lost consciousness or presented amnesia of the event and between 12 and 19% presented grand mal seizures[22,23].

The presence of recurrent neuroglycopenic symptoms, as in this case, warrants supervised testing to detect insulin-mediated causes of hypoglycaemia[22,23].

In the case of the report, the patient had neuroglycopenic symptoms and a convulsive state of great malice that requires admission to intensive care. And insulin and C-peptide levels were inappropriately elevated for plasma glycemia, raising the diagnosis of "hyperinsulinism hypoglycaemia" or hypoglycaemia with endogenous hyperinsulinism. Once the biochemical diagnosis has been established, the tumour causing insulin secretion must be located. Insulinomas can be single or multiple, localized or metastatic.

Although most are solitary tumours, approximately 10% of patients have multiple intrapancreatic tumours[14,24].

The vast majority (≥90%) of insulinomas remain localized in the pancreas[24,25].

Tumours are usually small, with an average size of about 1.5 cm and can sometimes be difficult to locate by preoperative imaging[26]. In this case there were two pancreatic lesions but the size was just over 4 cm the largest and that can speak of evolution time because he has been with episodes of hypoglycaemia or tumour aggressiveness for three years due to a potential for rapid growth.

The pathologic appearance alone cannot determine whether a tumour is likely to be indolent and confined to the pancreas, as opposed to aggressive and likely to metastasize. Therefore, extension outside the pancreas is used as a marker of aggressive clinical course and risk of future recurrence. A higher prevalence of MEN1 is suggested among patients with multiple tumours (25%) and metastatic disease (13%), compared to a prevalence of 7.6% in the general population (14). Others report that up to 5-10% of insulinomas are associated with MEN-1[27], so it is essential to rule it out in these patients. In our case, the presence of mild hypercalcemia and elevated PTH suggests a possible diagnosis of primary hyperparathyroidism (PPH). Although to confirm this, it is essential that vitamin D is in a range of sufficiency, since its deficiency can raise PTH levels secondarily. But hyperparathyroidism secondary to vitamin D deficiency usually does not cause an increase in PTH well above 100 pg/

ml, in this case it is much more. A finding that reinforces the suspicion of PPH is the lesion described in the neck ultrasound suggestive of parathyroid adenoma. In addition to osteonecrosis of the femur, it could be a possible consequence of PPH[28].

As stated above, the ideal for the localization of the insulinoma is ultrasound and computed tomography. In our case, the CT scan found the insulinoma and the PET scan was added as a complementary study.

The treatment of choice is surgery, which achieves cure in up to 90% of patients with benign insulinomas[4,5]. In the case of malignant insulinomas, surgery of the primary tumour increases survival between 12 and 28 months and allows better management of symptoms, although it is not curative[5].

Other therapeutic strategies include invasive procedures such as chemical or radiofrequency ablation or embolization of nutritive arteries, but there are also pharmacological therapies for symptomatic control such as glucose serum, diazoxide, somatostatin analogues, therapy with peptide receptor radionuclides (lutetium) or chemotherapy[4,5].

Medical treatment includes fractionation of the diet, somatostatin analogues, diazoxide and lutetium cone was raised in this case; but other drugs such as everolimus, sunitinib could also be used when the previous ones did not work.

Somatostatin analogues have been shown to not only improve symptoms and reduce tumour size in well-differentiated tumours, but also stabilize the progression of liver metastases in some cases.

In patients with somatostatin receptor-positive pancreatic neuroendocrine tumours, such as in this patient, if the disease is of low volume, initial treatment with a long-acting somatostatin analogue such as octreotide and lanreotide is suggested[29].

In those with symptomatic hepatic-predominantly low-volume disease, hepatic arterial embolization, chemoembolization or radioembolization may be used.

In our case, the patient had two pancreatic NETs and positive for somatostatin receptors demonstrated with PET, but of high volume, so the initial treatment options that can achieve a reduction in the disease burden include treatment with radionuclides of peptide receptors with positive somatostatin receptors, plus liver-directed therapy or capecitabine plus temozolomide that he did not receive. Since they had a PET scan that showed radiotracer uptake, they may benefit from treatment with these radiopharmaceuticals.

Treatment with long-acting somatostatin analogues may retard tumour growth in patients with locally advanced or well-differentiated somatostatin receptor-positive pancreatic NETs and for that reason it was used in this case[30].

In patients with locally advanced, unresectable or metastatic pancreatic NETs that are positive for somatostatin receptors, initial therapy with lutetium Lu-177 dotatate in combination with octreotide or lanreotide improves tumour response compared to high-dose octreotide[31]. For small (< 3 cm) neuroendocrine liver metastases, radiofrequency ablation, cryoablation, microwave ablation is most often used as an adjunct to surgical resection. Another suitable option for initial treatment in these advanced stages is liver-directed therapy, such as: hepatic arterial embolization, chemoembolization or radioembolization. However, the survival benefit of this treatment is less clear. In this case, it was performed, but then tried again without success, when the disease progressed (32).

Hepatic arterial embolization is frequently applied as a palliative technique in patients with a metastatic neuroendocrine tumour of hepatic predominance who are not candidates for surgical resection, which was the case in our case. It is based on the principle that liver tumours obtain most of their blood supply from the hepatic artery, while healthy hepatocytes obtain it from the portal vein[32].

In this patient, the expression of somatostatin receptors in the pancreas and in liver metastases allowed the use of lutetium, achieving a favourable initial response with reduction of hypoglycaemia and tumour stabilization. However, over time, the disease progressed, suggesting possible resistance to treatment. Like trans arterial embolization that was used, but in a second attempt it was not achieved.

When the patient began to present with recurrent hypoglycaemia despite the administration of subcutaneous octreotide every 8 hours, the possibility of a paradoxical aggravation of hypoglycaemia due to inhibition of the secretion of counterregulatory hormones was raised. However, this hypothesis was discarded, as hypoglycaemia persisted even after treatment was discontinued.

Conclusions

Insulinoma is the most common functional pancreatic neuroendocrine tumour that causes hyper insulinemic hypoglycaemia. Early diagnosis and intervention, particularly in patients with a history of neurological or psychiatric problems, postprandial symptoms or rapid improvement in symptoms after treatment, can lead to significantly better outcomes[18]. The therapeutic management of malignant insulinomas is complex and requires a multidisciplinary approach. Surgery is the treatment of choice in respectables cases; however, in advanced stages, as in this case, palliative strategies are used with the main objective of controlling symptoms and improving the patient's quality of life.

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