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GLP-1 RECEPTOR AGONIST ASSOCIATED UNMASKING OF INSULINOMA

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ABSTRACT

Background: Insulinoma is a rare functional pancreatic neuroendocrine tumour and the most common cause of endogenous hyperinsulinaemic hypoglycaemia in adults. Diagnosis is frequently delayed due to non-specific and intermittent symptoms, and a high index of suspicion is needed.

Case description: We report the case of a 40-year-old non-diabetic woman who presented with recurrent episodes of weakness shortly after initiation of a glucagon-like peptide-1 receptor agonist (GLP-1RA). Laboratory evaluation demonstrated inappropriately elevated insulin and C-peptide levels during documented hypoglycaemic events, consistent with endogenous hyperinsulinaemia. Autoimmune and exogenous causes were excluded. Imaging studies identified a 2 cm hypervascular pancreatic lesion, with functional imaging confirming somatostatin receptor avidity consistent with an insulin-secreting tumour. The patient was initially treated with diazoxide as a bridge to definitive management. She subsequently underwent laparoscopic distal pancreatectomy, with histopathology confirming a well-differentiated pancreatic neuroendocrine tumour (WHO Grade 1). Following surgery, hypoglycaemia resolved completely.

Conclusion: This case highlights the potential of GLP-1 receptor agonist therapy to unmask an insulinoma. Many benign insulinomas exhibit abundant expression of GLP-1 receptors. While a high index of suspicion remains essential, awareness of the emerging association between the incretin-based therapies and unexplained hypoglycaemia may facilitate earlier diagnosis.

KEYWORDS

Insulinoma, glucagon-like peptide-1 receptor agonists (GLP-1RAs), hypoglycaemia

LEARNING POINTS

- Hypoglycaemia is a rare but significant clinical event, and thorough evaluation is mandatory.
- Widely used GLP-1RA medications are glucose-dependent and therefore rarely cause hypoglycaemia; occurrence should prompt clinical suspicion for an underlying cause.
- Benign insulinomas express high levels of GLP-1 receptors; consequently, GLP-1 RAs may induce otherwise unexplained hypoglycaemia and can be used as tracers to localise difficult to detect tumours.

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INTRODUCTION

Insulinoma is a rare functional pancreatic neuroendocrine tumour that autonomously secretes insulin, leading to recurrent episodes of hypoglycaemia. It is the most common cause of endogenous hyperinsulinaemic hypoglycaemia in adults, with an estimated annual incidence of 1–4 cases per million individuals. Most insulinomas are solitary, benign and less than 2 cm in diameter. However, diagnosis is often delayed due to non-specific symptoms and intermittent glucose fluctuations.

Here, we present a case of a non-diabetic woman in whom initiation of GLP-1 receptor agonist therapy unmasked an undiagnosed insulinoma.

CASE DESCRIPTION

A 40-year-old woman, married with two children and employed in the high-technology sector, presented with a past medical history including hypothyroidism well controlled with levothyroxine, congenital glaucoma, polycystic ovary syndrome and previous gestational diabetes mellitus.

She presented to the emergency department with complaints of progressive generalised weakness, dizziness and perioral numbness that had developed over the past week. On arrival, she was haemodynamically stable and appeared well; physical examination was unremarkable. The blood glucose level on admission was 55 mg/dl.

On further history, the patient reported initiating subcutaneous semaglutide 0.25 mg weekly approximately two weeks before symptom onset, prescribed privately despite a BMI of 24 kg/m^2 and normal glycaemic status (HbA1c 4.4% two months earlier). After only one week, she self-increased the dose to 0.5 mg, shortly after hypoglycaemic symptoms had begun.

She was given a home glucometer due to a history of gestational diabetes. Using this device, she measured her blood glucose levels at home, which showed fasting values of 28–30 mg/dl. According to the patient, for most of her life her glucose levels had been around 70 mg/dl and tended to be lower mainly at night or after prolonged fasting.

Upon admission to the ward, she was kept on a liberal food intake, with instructions to report any hypoglycaemic symptoms.

Shortly after, a first suspicious clinical episode occurred with a glucose level of 63 mg/dl (on the glucometer). Blood measurements revealed plasma glucose of 45 mg/dl, insulin level of 456 pmol/l (range 17.8–173) and a C-peptide level of 900 pmol/l(range 370–1470). On a repeat clinical episode second laboratory test showed blood glucose level of 67 mg/dl, insulin 745 pmol/l and C-peptide 1295 pmol/l. Renal, liver, thyroid (thyroid-stimulating hormone 1.54 mIU/l) and adrenal function (morning cortisol 494 nmol/l, range 166–507) were normal.

After confirming hyperinsulinism, the primary consideration was to distinguish between exogenous and endogenous sources of hyperinsulinaemia. The patient denied use of exogenous insulin or any glucose-lowering medications; alcohol intake and other potential precipitating factors were excluded. Hypoglycaemic medication levels were ordered (but eventually was not followed through).

Given the absence of an apparent exogenous cause, an endogenous source of insulin excess was suspected. Within this group, the main possibilities included insulinoma and insulin autoimmune syndrome. To explore those possibilities, an abdominal CT and a comprehensive panel of insulin-related autoantibodies were ordered.

The following antibodies were all negative: insulin autoantibody, anti-insulin receptor antibody, glutamic acid decarboxylase, islet cell antibody, zinc transporter 8 and protein tyrosine phosphatase IA-2.

Contrast-enhanced CT of the abdomen revealed a 1.6 × 2.1 cm hypervascular lesion in the pancreatic body *(Fig. 1A)*. In addition, a 2.3 × 2.9 cm hyperenhancing lesion in the liver and a 3.8 cm mass in the caecum were identified. To further explore the nature of these findings as a spread from a potential pancreatic process we advanced to ^{68}Ga-DOTATATE PET/CT scanning, which revealed intense somatostatin receptor avidity confined to the pancreatic lesion, suggesting an insulin-secreting source. The hepatic and caecal lesions demonstrated no uptake *(Fig. 1B)*.

A colonoscopy was performed and the caecal lesion

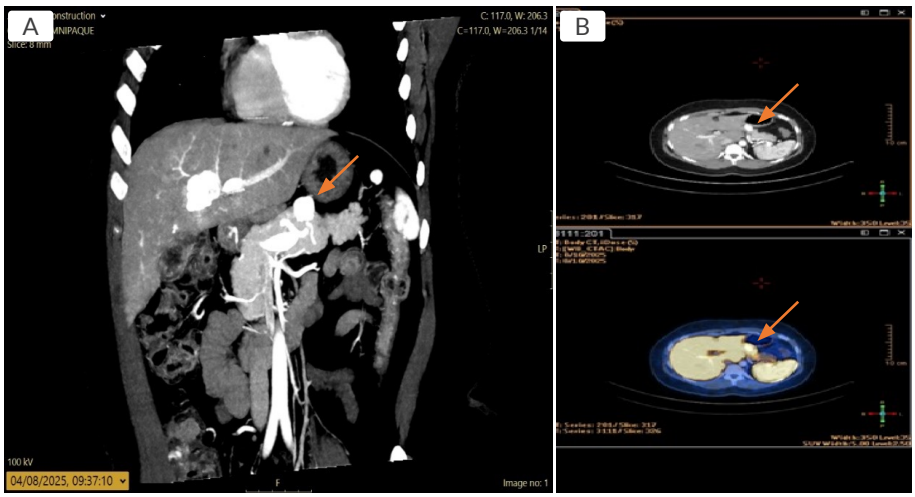


Figure 1. *A) Computed tomography with dual-energy technique, pancreas protocol, coronal section: in the arterial phase, within the body of the pancreas, a well-defined solid lesion is demonstrated, showing marked homogeneous enhancement in the arterial phase. B) ^{68}Ga-DOTATATE PET/CT: an exophytic nodule in the body of the pancreas demonstrates markedly increased uptake of somatostatin receptors.*

was resected, with later histopathological diagnosis of a tubulevillous adenoma with high-grade dysplasia.

After surgical consultation a liver/abdomen MRI was ordered to further characterise the hepatic findings. The examination demonstrated three well-circumscribed, hyperintense lesions with imaging features compatible with haemangiomas (the largest being 2.8 cm).

Parallel to establishing the source of hyperinsulinism, we first suggested frequent food consumption and later treated with intravenous dextrose 5% in water. Following the diagnosis of the pancreatic hypervascular lesion we started diazoxide 100 mg twice daily, which partially stabilised glucose levels and served as a bridge to definitive therapy.

Subsequently, the patient decided to go through the surgical procedure at another medical facility and underwent laparoscopic distal pancreatectomy with splenectomy and cholecystectomy.

Histopathology revealed a well-differentiated neuroendocrine tumour (WHO Grade 1) confined to the pancreas, without lymphovascular or perineural invasion.

Four months post-surgery the patient felt well, with no episodes of weakness.

DISCUSSION

Insulinoma is a rare functional pancreatic neuroendocrine tumour and the most common cause of endogenous hyperinsulinaemic hypoglycaemia in adults. Despite its typically benign nature, diagnosis is frequently delayed due to the intermittent and non-specific nature of presenting symptoms[1]. Glucagon-like peptide-1 receptor agonists, including newer dual agents such as the GLP-1/ glucose-dependent insulinotropic polypeptide (GIP)receptor agonist, are increasingly available and widely used for the treatment of type 2 diabetes mellitus and obesity, and are associated with a low risk of hypoglycaemia when used as monotherapy, reflecting their glucose-dependent insulinotropic action[2].

Fortunately, in our case, the patient's unexplained episodes of weakness were sufficient to raise a high index of suspicion for hypoglycaemia, albeit the temporal association between the initiation of low dose GLP-1 receptor agonist. Although rare and unlikely, the suspicion of hypoglycaemia prompted both her family physician and the admitting physician to pursue further investigation, ultimately leading to the diagnosis of a benign insulinoma.

Examining possible explanations for the GLP-1 receptor agonist unmasking an insulinoma revealed that pancreatic neuroendocrine tumours, mainly insulinomas often express incretin receptors including GLP-1 and GIP receptors, at high density. Other neuroendocrine tumours, such as duodenal neuroendocrine tumours, (but not gastrointestinal neuroendocrine carcinoma or pulmonary neuroendocrine tumours) and even pancreatic adenocarcinoma also express GLP-1 receptors[3-6].

It is well recognised in prospective and retrospective studies that labelled GLP-1 receptor analogues can be used for the detection of insulinomas, particularly outperforming ^{68}Ga-labelled somatostatin receptor scintigraphy when elusive or small insulinomas are sought[3,5-7].

The lack of GLP-1R expression in insulinomas was associated with impaired overall survival, larger tumour diameter, higher Ki-67 PI and weaker insulin staining[6,8]. Pharmacologic stimulation of tumoural incretin receptors by the GLP-1 receptor agonist may have enhanced autonomous insulin secretion from insulinoma cells, prompting clinical hypoglycaemic episodes and making the diagnosis earlier.

Several reports have described cases in which initiation of incretin-based therapy precipitated recurrent or severe hypoglycaemia, ultimately leading to the diagnosis of insulinoma[9]. Importantly, this unmasking phenomenon has been observed across different clinical contexts. Insulinoma detection following exposure to GLP-1 receptor agonists has been reported in both diabetic and non-diabetic individuals, including cases in which continuous glucose monitoring facilitated recognition of recurrent hypoglycaemia and prompted further diagnostic evaluation[10]. Additional reports have documented similar presentations in association with newer dual incretin therapies, such as tirzepatide. In these cases, hypoglycaemia was frequently disproportionate to expected pharmacologic effects and persisted despite treatment discontinuation, supporting the presence of autonomous insulin secretion and reinforcing the concept of pharmacologic unmasking rather than medication-induced hypoglycaemia[10].

In our case, the close temporal relationship between GLP-1 receptor agonist exposure and symptom onset supports the concept of pharmacologic unmasking of an insulinoma, as described in prior reports. Together with the previous observations this raises the possibility that, with the increasing use of potent incretin-based therapies, hypoglycaemic events may warrant a broader differential diagnosis and serve as an early clinical signal. This, in turn, may facilitate earlier biochemical confirmation and more targeted imaging, which could contribute to earlier recognition of insulinoma.

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