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Insulinoma after sleeve gastrectomy: A case report

Lobaton-Ginsberg M *et al.* Insulinoma after sleeve gastrectomy

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Abstract

BACKGROUND

Laparoscopic sleeve gastrectomy (LSG) has been proposed as an effective and durable treatment for severe obesity and glucose metabolism disorders, and its prevalence has increased from 5% to 37% since 2008. One common complication after bariatric surgery is a postprandial hyperinsulinemic hypoglycemic state. While rare, insulinomas can cause this state, where symptoms are more common in the fasting state; thus, evaluation of insulin secretion is needed. Until now, there have been no reports of insulinoma after LSG.

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CASE SUMMARY

We describe a case of 43-year-old women who was referred to the obesity clinic two years after LSG was performed. She had symptoms of hypoglycemia predominantly in the fasting state and documented hypoglycemia of less than 30 mg/dL, which are compatible with Whipple's Triad. Initially, dumping syndrome was suspected, but after a second low fasting plasma glucose was documented, a 72-h fasting test was performed that tested positive. Computed tomography and endoscopic ultrasound were performed, identifying the presence of a homogeneous hypoechoic semioval tumoral lesion in the pancreas. The diagnosis was compatible with insulinoma. After laparoscopic enucleation of insulinoma, the symptoms and hypoglycemia disappeared. The histopathological report described a well-differentiated grade 2 neuroendocrine

tumor with positive chromogranin and synaptophysin and Ki67 immunopositivity in 4% of the neoplastic cells.

CONCLUSION

Insulinoma after LSG is a rare condition, and clinicians must be aware of it, especially if the patient has hypoglycemic symptoms during the fasting state.

Key Words: Insulinoma; Hypoglycemia; Bariatric surgery; Glucagon-like peptide 1 amide; Neuroendocrine tumors; Case report

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Core Tip: Neuroglycopenic symptoms compatible with Whipple's triad were identified in women two years after laparoscopic sleeve gastrectomy, predominantly occurring in the fasting state. After discarding late dumping syndrome, a 72-h test was performed and tested positive. Imaging techniques documented the presence of a tumoral lesion in the pancreas, compatible with insulinoma. After laparoscopic enucleation of insulinoma, the symptoms were relieved. When hypoglycemia occurs after bariatric surgery, evaluation of insulin secretion is needed to conduct a correct diagnostic approach. Follow-up must be performed by a multidisciplinary team.

INTRODUCTION

The obesity pandemic has become a great topic of interest due its implications for quality of life, comorbidities, increasing mortality and the economic impact on health services worldwide^[1]. Bariatric surgery (BS) is an effective and durable treatment for severe obesity and glucose metabolism disorders, with laparoscopic Roux-Y gastric bypass surgery (RYGB) being the most common procedure^[2,3]. Nevertheless,

¹³ laparoscopic sleeve gastrectomy (LSG) has been proposed as a procedure capable of achieving the same goals, but with fewer complications^[4].

A common complication in BS is the development of a postprandial hyperinsulinemic hypoglycemic state^[5]. Hypoglycemia is defined as a glucose level below 70 mg/dL according to the American Diabetes Association guidelines^[6]. The possible causes of hypoglycemia in patients who had undergone BS include late dumping syndrome, nesidioblastosis and, rarely, insulinoma^[5,7]. Up to 40 cases of nesidioblastosis have been reported after RYGB, and only one case has been reported after sleeve gastrectomy^[8,9]. To our knowledge, there are few reports of insulinoma after BS^[10] but no reports after LSG. The purpose of these case reports is to inform clinicians that patients with neuroglycopenic symptoms during the fasting state could have hypoglycemia caused by insulinoma, which is not only due to late dumping syndrome.

¹ A review of the medical literature for insulinoma and hypoglycemia after BS was performed in PubMed. We searched “insulinoma”, “hypoglycemia”, “sleeve gastrectomy”, “RYGB”, “glucagon-like peptide 1 (GLP-1)” and “ghrelin” and a combination of the above terms including all dates up to October 2021. Herein, we present a case of a 43-year-old woman referred to the obesity clinic due to neuroglycopenic symptoms caused by an insulinoma two years after a sleeve gastrectomy.

⁴ **CASE PRESENTATION**

Chief complaints

A 43-year-old woman was referred to the obesity clinic due to neuroglycopenic symptoms caused by an insulinoma two years after a sleeve gastrectomy.

History of present illness

In March 2020, two years after LSG was performed, the patient developed neuroglycopenic symptoms including short-term memory loss, lingual nerve paresthesia and nonspecific visual alterations predominantly during the morning in a

fasting state. These symptoms were suppressed with food intake. Two months later, she visited a physician who documented fasting plasma glucose of 27 mg/dL, and in June 2020, the symptoms occurred more frequently, and she gained 14 kg. In the beginning, late dumping symptoms were suspected, but in September 2020, fasting plasma glucose of 30 mg/dL was documented, so she was hospitalized for the evaluation of hypoglycemia in a 72-h supervised fast test. She had baseline plasma glucose of 67 mg/dL, nonsuppressed insulin of 16.4 IU/mL and C-peptide of 3.64 ng/mL. In the first hour after initiation, she developed Whipple's triad symptoms, and her lab results detected plasma glucose of 38 mg/dL, insulin of 25.9 IU/mL and C-peptide of 4.31 ng/mL. Thus, it was decided to stop the protocol and initiate 1000 mL of 20% glucose solution in 12 h.

History of past illness

In 2002, she was diagnosed with obesity and dyslipidemia (high triglycerides and cholesterol with low high Density Lipoprotein) and treated with improvements in diet, physical activity and statins without weight control. In 2016, a gastric balloon was placed, and although her body mass index (BMI) in 2018 was 34.4 kg/m², LSG was performed.

Personal and family history

She had no specific personal or family history.

Physical examination

After LSG, she weighed 74 kg, and her BMI was 32 kg/m². The physical examination showed no obvious cardiovascular or respiratory abnormalities. The abdomen was soft, and the only sign was the presence of postsurgery scars.

Laboratory examinations

Upon hospitalization prior to the surgery, her hemoglobin A1c level was 4.8% (normal range: < 5.7%). The C-peptide values were normal at 3.64 ng/mL (1.1-4.4 ng/mL), and insulin was mildly elevated at 16.4 µUI/mL (3.21-16.3 µUI/mL). Lipid levels indicated dyslipidemia with total cholesterol of 224 mg/dL and LDL-c of 142.8 mg/dL. Other biochemical parameters were normal and only an iron deficiency anemia was documented. Thyroid function was normal, with TSH 2.46 µUI/mL (0.27-4.2 µUI/mL), FT4 1.06 ng/dL (0.93-1.7 ng/dL), and cortisol 15.04 µg/dL (3.7-19.4 µg/dL) levels within the normal range.

Imaging examinations

Computed tomography (CT) demonstrated the presence of a focal asymmetric reinforcement area in the head of the pancreas (Figure 1A). Endoscopic ultrasound showed the presence of a tumoral lesion in the pancreas in close proximity to the main pancreatic duct and splenomesenteric confluence without evidence of invasion (Figure 1B and C).

FINAL DIAGNOSIS

The final diagnosis was insulinoma. This was confirmed with histology and immunohistochemistry of the tumor (Figures 2).

TREATMENT

After a surgery consultation, a laparoscopic insulinoma enucleation was performed without complications. No other tumors were identified in the upper abdomen.

OUTCOME AND FOLLOW-UP

Histopathological findings revealed a well-differentiated neuroendocrine grade 2 tumor with free edges. Immunohistochemical studies confirmed positive chromogranin and synaptophysin as well as a proliferative activity (Ki67) in 4% in neoplastic cells.

After surgery, the neuroglycopenic symptoms were relieved, and she had no hypoglycemic events. Her current treatment is diet and physical activity, targeting a BMI of 31.1 kg/m².

DISCUSSION

Since 2013, 468,609 BSs have been performed worldwide^[2]. LSG was initially introduced as a first-stage restrictive procedure to a more complex definitive one. At present, it is performed as a stand-alone BS^[7]. Since 2008, the prevalence of the LSG procedure has increased from 5% to 37% worldwide^[2], but in Mexico, it is performed only in 13% of patients, whereas LRYGB is performed in 85.8%, with a bypass/sleeve ratio of 7:1. In our center LSG accounts for 20% of total BS (200 procedures since 2010).

LSG comprises vertical longitudinal resection of the greater gastric curve that includes the fundus, body and antrum as well as the formation of a tubular conduit with a capacity of < 100 mL. Weight loss is achieved by restrictive and humoral effects^[8,11].

Hypoglycemia is a well-documented complication after BS. Papamargaritis *et al*^[12,13] recorded a study where 33% of patients experienced severe hypoglycemia a year after LSG due to late dumping symptoms, which usually occurs 1-3 h after a high-carbohydrate meal triggering a hyperinsulinemic response. Since 2005, up to 40 cases of nesidioblastosis after RYGB have been reported^[8], and only one case after LSG was documented in 2019 by Kim *et al*^[9]. While rare, insulinomas have been reported after BS. Mulla *et al*^[10] described 7 cases of insulinoma, one patient with pancreatic neuroendocrine tumor and one patient with insulinoma and pancreatic neuroendocrine tumor after BS, 78% of whom were women. In this cases hypoglycemia was more common in the fasting state.

The mechanism of the post-BS hyperinsulinemic hypoglycemic state and the changes in beta cell proliferation are not fully understood. In the LSG, the faster transit of undigested nutrients to the distal gastrointestinal tract due to rapid gastric emptying upregulates GLP-1 production secreted by enteroendocrine L cells in the distal intestine.

This increase can normalize blood glucose and regulate insulin synthesis and proinsulin gene expression, as well as glucagon and somatostatin secretion^[3]. GLP-1 has multiple beneficial effects on β cells, including an increase in their number by inhibiting apoptosis and enhancing neogenesis as well as promoting its proliferation. In a study carried out in 2016 by Xu Fa *et al*, it was found that a chemically modified GLP-1 (mGLP-1) analog promotes the proliferation of pancreatic mouse β cells, upregulating the expression of *cyclin E*, *CDK2*, *Bcl-2*, *Bax* and *p21*. The *cyclin E*-CDK2 complex plays an important role in the regulation of the G1 phase of the G1/S cell cycle, while *p21* is a universal cyclin-dependent kinase (CKI) inhibitor. Meanwhile, the *Bcl-2* and *Bax* genes, two important members of the *Bcl-2* gene family, have opposite functions, inhibiting or promoting cell apoptosis, respectively^[14].

An increase in ghrelin levels has been observed a year after BS^[15]. Ghrelin and the type 1a ghrelin receptor (GHS-R1A) are expressed in different types of neuroendocrine tumors. Recently, Hain Hu *et al*^[16] found that GHS-R1a was found in 60% of insulinomas, suggesting that ghrelin may act through autocrine or paracrine pathways. The proliferative effects of ghrelin and its association with insulinoma have not been studied, although there is a clinical case report where a ghrelin-producing neuroendocrine tumor was transformed into an insulinoma^[17].

The diagnosis of hypoglycemia after BS is challenging. The first step after identifying the presence of symptoms is to verify their relationship to hypoglycemia. A detailed clinical history must be performed to identify family or personal history of neuroendocrine tumors, if patients are taking any hypoglycemic medication such as sulfonylureas or if the symptoms are more common in fasting state, as in our case.

In a stepwise manner, biochemical analysis must be performed to rule out other causes^[18]. Plasma glucose, insulin, C-peptide, proinsulin, betahydroxybutyrate and cortisol levels should be measured. The development of provocative studies such as a 72-h fasting test is also recommended^[10,18]. The goal is to determine whether beta-cell peptides are appropriately suppressed during hypoglycemia. If autonomous insulin secretion is identified, insulinoma should be suspected^[10,18]. The next step is to

determine the anatomical localization and to exclude other tumors. Multidetector contrast-enhanced imaging CT or dual phase helical CT with thin sections are the preferred initial imaging options. In patients in whom noninvasive radiologic techniques are negative or to improve the sensitivity for identifying an insulinoma, endoscopic ultrasound (EUS) must be performed. EUS has 80-92% sensitivity for detecting tumors as small as 5 mm. Additionally, EUS-guided fine needle aspiration (FNA) allows pathologic confirmation in 57% of patients. If the techniques mentioned above fail to detect the tumor, selective arteriography and intra-arterial calcium stimulation tests with hepatic venous sampling can be performed. They should be used only as a last resort because they are invasive techniques^[5,10]. In our case, we performed CT and EUS that allowed us to identify insulinoma.

Finally, histopathologic and immunohistochemical confirmation is necessary to classify the type of tumor and to determine the patient's follow-up^[19].

The definitive treatment for insulinoma comprises surgical complete resection. However, there are other treatment options such as octreotide or EUS-guided alcohol tumor ablation, radiofrequency ablation (RFA) or embolization^[20]. There is superior short-term recovery, shorter length of stay, decreased hemorrhage and improved cosmesis when performing minimally invasive pancreatic resection compared to open pancreatic surgery^[10]. However, the technique used depends on the size, extension, localization and type of lesion. Atypical resection, including enucleation and partial or middle pancreatectomy, has the advantage of pancreatic parenchyma preservation, thereby reducing the risk of late exocrine and/or endocrine insufficiency^[20]. As in the case of our patient, when the lesion was small, benign, solitary, superficial and when the pancreatic duct was not involved, the best surgical approach was laparoscopic enucleation^[21]. It is important to note that positive resection margins are not associated with increased recurrence rates^[10].

CONCLUSION

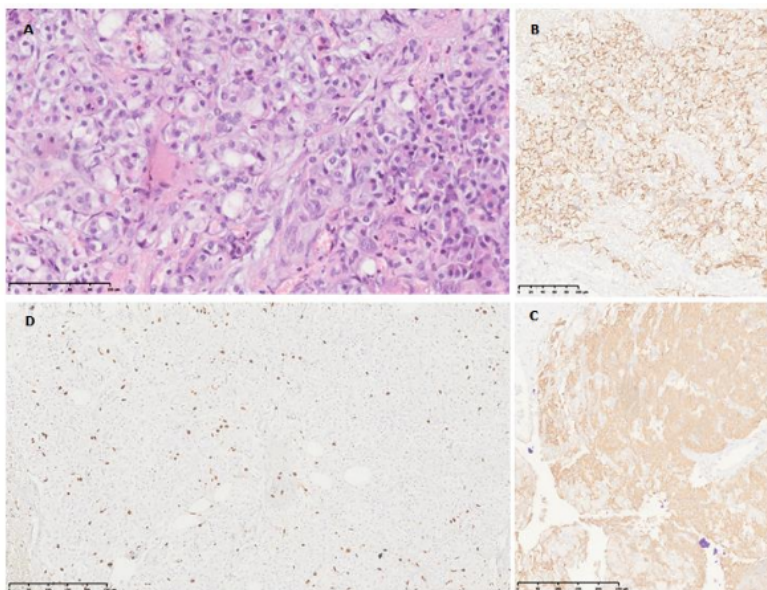
This is the first case of insulinoma after sleeve gastrectomy. Although this is a very rare case; clinicians must be aware of it, especially if the patient has hypoglycemic symptoms during the fasting state.

Figure Legends



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Figure 1 Imaging examinations. A: Computed tomography protocol for neuroendocrine tumors. The red arrow indicates a focal asymmetric reinforcement area of 11 × 14 mm of 145 HU in the head of the pancreas; B and C: Endoscopic ultrasound indicating the presence of a homogeneous hypoechoic semioval tumoral lesion in the pancreas, with well-defined borders measuring 2.1 × 1.2 cm, in close apposition to the main pancreatic duct and splenomesenteric confluence without evidence of invasion.



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Figure 2 Histology and immunohistochemistry of the tumor. A: Hematoxylin and eosin photomicrograph (40 ×), neoplastic cells presenting uniformly round nuclei with granular chromatin (salt and pepper image), typical of neuroendocrine cells with extensive eosinophilic cytoplasm; B and C: Photomicrographs of immunohistochemical staining of chromogranin (B) and synaptophysin (C) 10 ×, neoplastic cells show strong immunopositivity for both markers in the cytoplasm, which corroborates the neuroendocrine lineage of the neoplasia; D: Immunohistochemical staining of Ki67 (cell proliferation index), strong nuclear immunopositivity is seen in approximately 4% of neoplastic cells. The tumor was classified as grade 2, according to WHO 2019.

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