

Insulinoma After Bariatric Surgery: Tricks for Diagnosis and Therapeutic Approach

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1. Abstract

1.1. Context: Hypoglycemia is a known late complication of bariatric surgery. Usually, it presents as postprandial episodes probably related to dietary transgressions. However, in some cases, patients show fasting episodes and an insulinoma must be ruled out.

1.2. Case Description: A 48-year-old Caucasian woman started few days after a sleeve gastrectomy with fasting episodes of cold sweating and anxiety that progressed rapidly to loss of consciousness. Biochemical evaluation 4 months post-surgery confirmed by a fasting test endogenous hyperinsulinism secretion [plasma glucose: 26 mg/dL, plasma insulin: 4.6 uU/mL and plasma C Peptide: 775 pmol/L]. Endoscopic ultrasonography [EUS] showed a lesion in the body of the pancreas. A distal pancreatectomy was performed and a G1 neuroendocrine tumor [NET] diffusely immunoreactive for insulin was resected. The patient remains asymptomatic after 36 months of follow up.

1.3. Conclusion: Insulinoma rarely occurs in the context of a bariatric surgery, only a few cases have been reported. The detection of hypoglycemic episodes and their relationship with meals are essential to guide the diagnosis.

2. Introduction

Hypoglycemia is a known late complication of the bariatric surgery [1], after both Roux-en-Y gastric bypass [RYGB] and sleeve gastrectomy. Its real prevalence is probably underestimated. A wide range, between 0.1-36% has been reported depending on the methodology used in the different studies [2,3]. Clinical presentation of post-bariatric hypoglycemia ranges from asymptomatic to mild autonomic symptoms, as palpitations or sweating, to more severe neuroglycopenic symptoms including confusion, blurred vision and even seizures or syncope. Typically, symptoms start 1-5 years after surgery, and they occur during the postprandial period [1-3 hours after meal]. The presence of recurrent hypoglycemia episodes in postoperative patients may be exacerbated by dietary transgressions [4]. The pathophysiology of hypoglycemia after a bariatric surgery is still incompletely understood. Several mechanisms seem to contribute to glucose deregulation in these patients, including a more rapid nutrient transit from the gastric pouch to the gut and an exaggerated increase meal induced-GLP1 response, dysfunction of β -cell and α -cells, adipokines, changes in gut microbiota, among others, all of which result in a disproportionate insulin response to food intake [5].

However, those patients with fasting hypoglycemia episodes, hypoglycemia occurring early after bariatric surgery [e.g., <6 months], or other atypical features, should need additional evaluation to exclude the rare occurrence of an insulinoma in the context of bariatric surgery [6]. Insulinoma is a rare insulin-producing islet cell tumor characterized by hypoglycemia episodes. Characteristically, these episodes are present during fasting. The suspicion of an insulinoma constitutes a major diagnostic challenge in the context of bariatric surgery because the symptoms of hypoglycemia are frequently misinterpreted or even attributed to the hypoglycemia that the surgery itself can cause. The coexistence of an insulinoma in a patient with a bariatric surgery is extremely infrequent and only a few cases have been reported. Here we presented a new case of hypoglycemia due to an insulinoma diagnosed after a sleeve gastric surgery for morbid obesity and we performed a review of similar cases reported in the literature.

3. Case Report

We reported a 48-year-old Caucasian woman with episodes of cold sweating, anxiety and confusion during fast that was referred to our institution. The symptoms began few days after laparoscopic sleeve gastrectomy for morbid obesity [BMI 52], performed 4 months before admission. Surgery and postoperative period were without complications with a weight loss of 35 kg. However, symp-

toms increased gradually in frequency and severity during the following months, predominantly during the morning, before breakfast, with several episodes of loss of consciousness that required hospitalization, where low plasma glucose levels were documented, and symptoms reversed after glucose administration. The initial evaluation in our institution included a 72 hs fasting test. She developed symptoms of neuroglycopenia [confusion and fatigue] 5 hours after the last meal, associated with plasma glucose level of 26 mg/dl, plasma insulin level of 4.6 [Normal Range 3-25 uU/mL] and plasma C Peptide level of 775 [NR 298-2350 pmol/L], indicating the endogenous hyperinsulinism. Endoscopic ultrasonography [EUS] showed an isoechogenic lesion in the body of pancreas with homogeneous blue elastography, suggestive of neuroendocrine tumor (Figure 1A). During the laparoscopic approach, intraoperative ultrasonography confirmed the lesion, and a distal pancreatectomy was performed. The lesion was found to be a well-differentiated tumor of 15x14x13 mm. Immunohistochemical studies showed positive staining for insulin, synaptophysin, chromogranin A and CK AE1/AE3, showing a ki 67 index of 2.8% and a mitosis count <1, leading to the diagnosis of a grade 1 neuroendocrine tumor based on the 2010 WHO Classification for Pancreatic Endocrine Neoplasms. However, the presence of vascular lymphatic embolisms (Figure 1 B) indicated a malignant insulinoma.

The patient remains asymptomatic after 36 months of follow up.

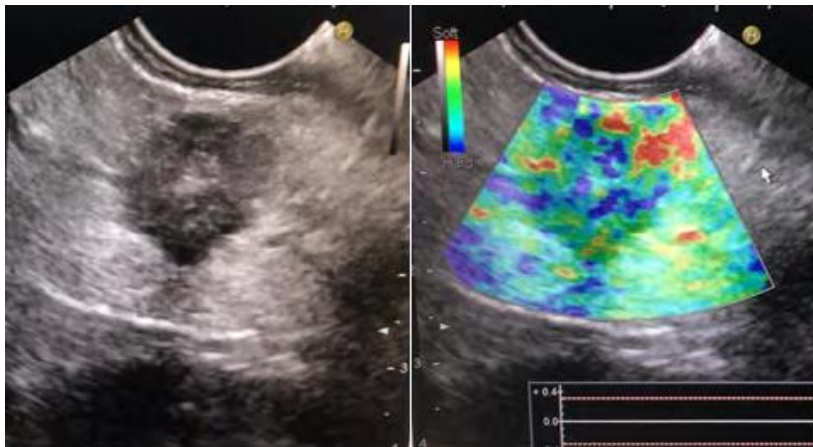


Figure 1: Endoscopic ultrasonography showed an isoechogenic lesion with regular border in the tail of the pancreas of 13x10mm, with a homogeneous blue elastography.

4. Discussion

We presented a new case of insulinoma in a patient with severe neuroglycopenic symptoms after a laparoscopic sleeve gastrectomy. Although the insulinomas is the most common cause of hyperinsulinemic hypoglycemia it is a rare functioning neuroendocrine tumor of the pancreas with an incidence of 1-4 cases per million. Classically, insulinoma is characterized by fasting episodes of hypoglycemia, even though postprandial hypoglycemia has been reported in ~ 10% of patients with insulinoma. Typically, insulinoma is a sporadic small benign tumor; malignancy or association with multiple endocrine neoplasia [MEN 1] is seen in less than 10%–15% of all cases [7]. The insulinoma- induced hypoglycemia after

bariatric surgery is an extremely unusual situation and only few cases have been reported. Nevertheless, the real incidence of this association is probably underestimated owing to the difficulties in differentiate the symptoms of the insulinoma from those caused by the metabolic alterations produced by the bariatric surgery itself. Both situations present with autonomic and/or neuroglycopenic symptoms, but the pattern of clinical presentation of hypoglycemic episodes may help to differentiate between them. Hypoglycemia post bariatric surgery is characterized by postprandial hypoglycemic episodes. The pathophysiology of this syndrome remains poorly understood and the reason why hyperinsulinemic hypoglycemia develops only in a subset of patients who have un-

dergone gastric bypass surgery is still unknown. Some preoperative factors has been reported to be associated to an increased risk of post-bariatric hypoglycemia, as the female sex, a RYGB surgery, a longer time since surgery, pre-operative symptoms of hypoglycemia or the lack of history of diabetes previous surgery [8,9]. However, hypoglycemic episodes have also been reported after a subtotal esophagectomy with partial gastrectomy, Billroth II [10], fundoplication, sleeve gastrectomy [11] and gastric banding [12] suggesting a functional basis of this disorder rather than to the pancreatic changes seen in these patients. The pathologic features of the pancreas from hypoglycemic post-bariatric patients remind to those reported in the noninsulinoma pancreatogenous hypoglycemia syndrome [NIPHS], an unusual form of endogenous hyperinsulinemic hypoglycemia. NIPHS is an extremely rare condition that also results in postprandial hypoglycemia, and it is characterized by beta cell hypertrophy, islets with enlarged and hyperchromatic nuclei, and increased islets budding from periductular epithelium [13,14]. Although, the pathology changes of NIPHS and post-gastric bypass hypoglycemia can be similar, the latter is considered a separate clinical entity that disrupt the regulation of gastric emptying and where the increased β -cell mass does not seem be the dominant contributor to post-bariatric hypoglycemia. This is support by the finding that reduction in β -cell mass by partial pancreatectomy has not been effective in fully resolving hypoglycemia over time in post-bariatric patients [6], while hypoglycemic symptoms have been well palliated after pancreatectomy in NIPHS [15].

The occurrence of autonomic symptoms of hypoglycemia could be complex to distinguish between symptoms of hypoglycemia and those due to dumping syndrome. The dumping syndrome is characterized by gastrointestinal and vasomotor symptoms, like abdominal pain, flushing, sweating, tachycardia and hypotension appeared during the first hours after eating. This syndrome is related to the alteration in the anatomy by surgery and/or the disturb of the intrinsic innervations that modifies the gastric emptying mech-

anism. This results in undigested food reaching the small intestine too quickly [16] and triggering a rapid fluid shift from the plasma compartments to the intestinal lumen, resulting in abdominal and vasomotor symptoms, but hypoglycemia was not documented.

In this paper we reported a new case of insulinoma related to bariatric surgery. Only sixteen cases were previously reported. (Table 1) shows the cases of insulinoma in context of bariatric surgery reported in the literature during the last fifteen years. The predominance of female cases probably is due to fact that the bariatric surgery is more common in women [17]. It is interesting to remark that almost patients showed the characteristic pattern of fasting hypoglycemia in contrast with the typical postprandial episodes caused by the bariatric surgery itself. Some patients manifested hypoglycemic symptoms before bariatric surgery while others started few weeks or months after it, as the case of our patient. It is probably that the insulinoma developed before bariatric surgery and the insulin resistance associated to the obesity was unmasking the hypoglycemic symptoms. Adipose tissue releases different products, as free fatty acid and inflammatory products like TNF α , IL-1 and IL-6, which contribute to both peripheral and hepatic insulin resistance [18], and which could counteract symptoms of insulin excess. Preoperative hyperinsulinemia and defective insulin action, normalize shortly after bariatric surgery [19], probably associated to weight loss during the perioperative period and mainly after bariatric surgery, facilitating the perception of symptoms of hypoglycemia and exposing the long-standing hyperinsulinism [6,19]. One of the describe cases were related to multiple endocrine neoplasia, found after the diagnosis of the insulinoma [20].

Insulin resistance caused by the obesity as well as lack of awareness of symptoms of hypoglycemia by the patients, may contribute to the delay in the identification of the insulinoma. Patients often fail to recognize autonomic warning symptoms and the hypoglycemia is only detected through the presence of neuroglycopenic symptoms delaying the diagnosis of the insulinoma for up to 5 years [21-37].

Table 1: Insulinoma and gastric surgery in the published literature, in the last 15 years.

Author	Age	Sex	Surgery	Symptoms onset	Symptoms and forms of presentation	Tumor size	Pathology
Zagury 2004 (19)	65	F	Gastric sleeve	Postoperative	FH, PPH	20mm	Insulinoma
Carpenter 2005 (11)	54	F	RYGB	2 years postoperative	FH, neuroglycopenic symptoms	NA	Insulinoma
Abellán 2007 (21)	51	M	RYGB	6 months postoperative	FH and PPH, adrenergic and neuroglycopenic symptoms	17mm	Insulinoma with nesidioblastosis
Seshadri 2008 (22)	61	F	LAGB	Preoperative	FH and PPH, adrenergic symptoms	12mm	Insulinoma
Guimaraes 2015 (23)	54	F	RYGB	2 years postoperative	PPH, adrenergic and neuroglycopenic symptoms	18mm	Insulinoma
Duff 2016 (24)	67	M	RYGB	Postoperative	FH and PPH	26mm	Insulinoma G1
Mulla 2016 (25)	45	F	RYGB	Preoperative	FH and PPH, adrenergic and neuroglycopenic symptoms	21mm	Insulinoma G1
Rose 2017 (26)	54	F	Sleeve Gastrectomy	Preoperative	FH, adrenergic and neuroglycopenic symptoms	16mm	Insulinoma

Søjbjerg 2018 (27)	48	F	RYGB	4 years postoperative	FH	NA	Insulinoma G1
Maloletkina 2019 (28)	53		RYGB	Preoperative	FH neuroglycopenic symptoms	20mm	Malignant insulinoma
Wehbeh 2019 (29)	69	F	RYGB	9 years postoperative	FH and PPH neuroglycopenic symptoms	14mm	Malignant insulinoma
Bones 2020 (30)		F	RYGB	>6 months postoperative	FH neuroglycopenic symptoms	20mm	Insulinoma
Sneineh 2020 (31)	37	F	RYGB	6 years postoperative	PPH, neuroglycopenic symptoms	18mm	Insulinoma
Lanpher 2021 (32)	74	M	RYGB	>1 year postoperative	FH		insulinoma
Poku 2021 (20)	48	F	Sleeve Gastrectomy	1 year postoperative	FH	16mm	Malignant insulinoma
Szczepanski 2021 (33)	67	F	RYGB	15 years	FH, adrenergic and neuroglycopenic symptoms	8mm	Insulinoma
Lobaton-Ginsberg 2022 (34)	43	F	Gastric sleeve	2 years	FH, neuroglycopenic symptoms	21mm	Insulinoma G2
Poku 2022 (35)	49	F	Gastric sleeve	1 year	FH, neuroglycopenic symptoms	16mm	Malignant insulinoma (MEN1)
Papamargaritis 2022 (36)	49	F	Gastric sleeve	Postoperative	FH, adrenergic and neuroglycopenic symptoms	16mm	Insulinoma G1
Teke 2023 (37)	62	F	Transit bipartition	Postoperative	FH and PPH, neuroglycopenic symptoms	15mm	Insulinoma G1
Barrio Löwer Daniele 2023	48	F	Sleeve Gastrectomy	Few days after surgery	FH and PPH, neuroglycopenic symptoms	15mm	Malignant insulinoma

F: Female, FH: Fasting hypoglycemia, G1: grade 1, LAGB: Laparoscopic adjustable gastric band, M: Male, NA: not available, PPH: postprandial hypoglycemia, RYGB: Roux-en-Y gastric bypass.

5. Conclusion

Insulinoma rarely occur in the context of a bariatric surgery, only a few cases had been reported. Insulinoma represents a challenge in the differential diagnosis of hypoglycemia after bariatric surgery. The detection of hypoglycemic episodes and their relationship with meals are essential to guide the diagnosis and treatment.

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