

## CASE REPORT

# Metastatic insulinoma presenting after bariatric surgery in a patient diagnosed with MEN1

Caroline Poku  | Hafsa Amjed | Fatima Kazi | Shanika Samarasinghe

Department of Medicine, Division of Endocrinology, Loyola University Medical Center, Maywood, Illinois, USA

**Correspondence**

Shanika Samarasinghe, Loyola University Medical Center, 2160 S. First Ave, Fahey Building Rm 137, 60153 Maywood, IL, USA.  
Email: ssamarasinghe@lumc.edu

**Funding information**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. There are no conflicts of interest to report

**Abstract**

Insulinomas are uncommon neuroendocrine tumors and metastatic disease is extremely rare. We report a patient with metastatic insulinoma associated with multiple endocrine neoplasia type 1 presenting with hypoglycemia following sleeve gastrectomy. Potential causes of hypoglycemia include dumping syndrome, non-insulinoma pancreatogenous hypoglycemia syndrome, and rarely insulinoma. MEN1-associated insulinomas have a higher recurrence rate.

**KEYWORDS**

hypoglycemia, insulinoma, metastatic insulinoma, multiple endocrine neoplasia type 1

## 1 | INTRODUCTION

We present a rare case of a patient with a history of bariatric surgery diagnosed with metastatic insulinoma and multiple endocrine neoplasia type 1 (MEN1) 2 years after sleeve gastrectomy. Insulinomas are characterized by fasting hypoglycemia with neuroglycopenic symptoms. Insulinomas are rare neuroendocrine tumors with a reported incidence of 4 cases/million/year, infrequently they are metastatic and carry a poorer prognosis.<sup>1</sup> To the best of our knowledge, this is the second reported case of metastatic insulinoma presenting after bariatric surgery.<sup>2</sup>

## 2 | CASE PRESENTATION

A 49-year-old woman with a past medical history of hypertension, depression, polycystic ovarian syndrome, primary hyperparathyroidism s/p 3.5 gland parathyroidectomy in

2008, facial angiofibroma s/p resection in 2011, obesity s/p gastric sleeve 2018, and a history of diabetes mellitus (DMT2) presented with frequent episodes of hypoglycemia. DMT2 was diagnosed in 2003 with an A1c of 8% and managed initially with metformin and subsequently with exenatide. Laboratory data in 2016 documented an HgbA1c of 6.6% with a fasting glucose of 141. Prior to her bariatric surgery in 2018, her A1c was 6.1% and 6 months after gastric sleeve her A1c was 5.1%. All hypoglycemic agents were withdrawn at the time of sleeve gastrectomy.

The patient initially lost 36 kg following her bariatric surgery. One year after surgery, she started to develop frequent, primarily fasting hypoglycemia in the 40–50 mg/dl range confirmed on continuous glucose monitoring (CGM) (Figure 1). Symptoms included perioral numbness, diaphoresis, and confusion, which resolved with glucose tablets. She reported a 7 kg weight regain due to eating every 2 h to minimize episodes but symptoms progressed. She was initially able to manage her hypoglycemic

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

### AGP Report

July 2, 2020 - July 29, 2020 (28 Days)

LibreView

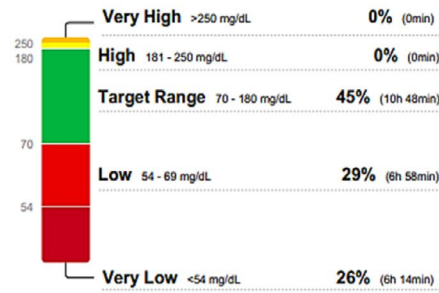
#### GLUCOSE STATISTICS AND TARGETS

July 2, 2020 - July 29, 2020 **28 Days**  
 % Time CGM is Active **91%**

Ranges And Targets For	Type 1 or Type 2 Diabetes
<b>Glucose Ranges</b>	<b>Targets % of Readings (Time/Day)</b>
Target Range 70-180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h)
Above 250 mg/dL	Less than 5% (1h 12min)

Average Glucose **73 mg/dL**  
 Glucose Management Indicator (GMI) **5.1%**  
 Glucose Variability **37.8%**  
 Defined as percent coefficient of variation (%CV); target ≤36%

#### TIME IN RANGES

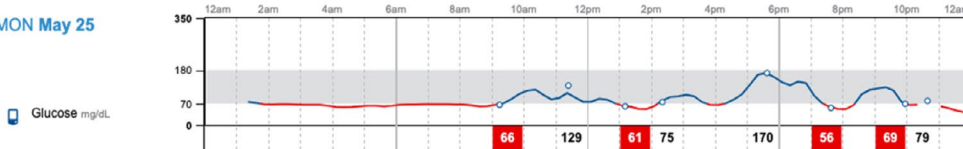


### Daily Log

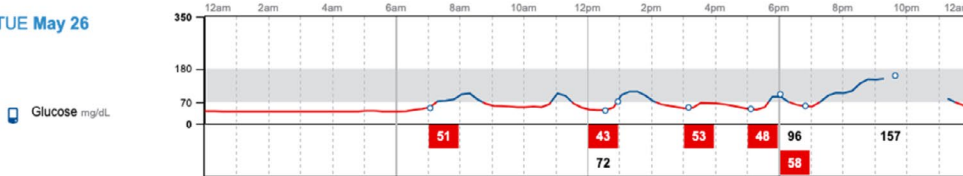
May 20, 2020 - June 16, 2020 (28 Days)

LibreView

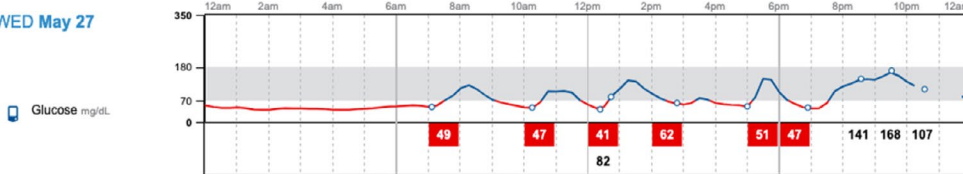
MON May 25



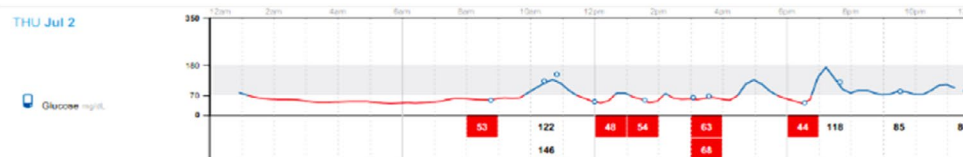
TUE May 26



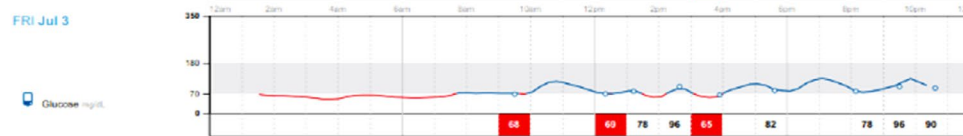
WED May 27



THU Jul 2



FRI Jul 3



SAT Jul 4



SUN Jul 5



FIGURE 1 Continuous glucose monitoring documenting recurrent episodes of severe hypoglycemia

symptoms with frequent meals, however, symptoms progressed to the point that she had several emergency room visits with low glucose levels documented into the 30 mg/dl range.

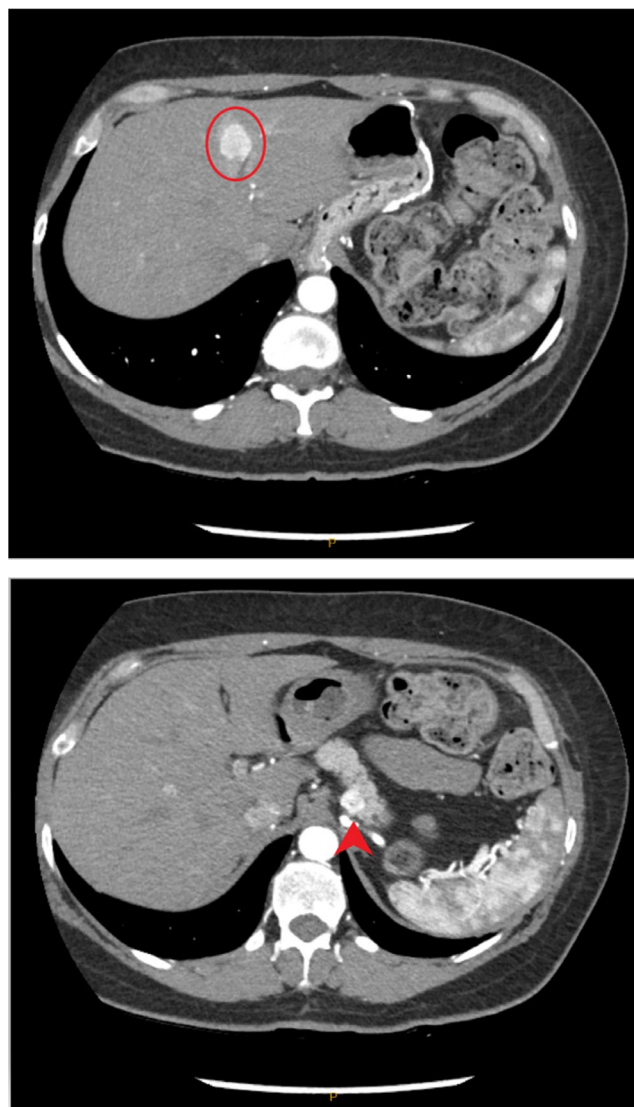
Her family history was significant for hypertension, diabetes, and coronary artery disease. Her mother had a history of bone cancer. Of significance, she reported her sister had passed away in her sleep at age 47 of unknown causes. An autopsy was not completed. The patient's physical examination was significant for a fleshy papule noted on her left cheek.

### 3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND TREATMENT

Investigation during a previous hospitalization included a normal cosyntropin stimulation with peak cortisol of 24.9 mcg/dl. She was noted to have mild prolactin elevation with a prolactin of 36.2 ng/ml (4.79–23.30 ng/ml) with a history of regular menses. Intermittent hyperparathyroidism was documented from 61–89 pg/ml (15–65 pg/ml) with calcium ranging from 9.9 to 10.8 mg/dL and a mildly low phosphorus at 2.3 mg/dl (2.5–4.5). Additional biochemical evaluation included IGF-1 level of 140 ng/ml, TSH 1 uIU/ml, FT4 1.4n g/ml, and a hemoglobin A1c of 4.8% (0%–5.6%).

At this time, the differential was late dumping syndrome, noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS), or most likely insulinoma. She was admitted for a 72 h fast, which confirmed hyperinsulinemia with symptomatic hypoglycemia at a serum glucose of 37 mg/dl approximately 2 h into the fasting period. Concurrent data demonstrated a suppressed  $\beta$ -hydroxybutyrate of 0.6 mmol/L, insulin 2 mU/L, elevated proinsulin 7.7  $\mu$ mol/L, and inappropriately normal c-peptide 0.8 ng/ml. The oral hypoglycemic panel was negative. VIP, gastrin, and glucagon levels were negative. Chromogranin A was elevated at 145 ng/ml (0–103). A pancreatic protocol CT revealed a 1.2 cm heterogeneous arterial enhancing lesion in the body of pancreas, a 0.6 cm focus in the tail of pancreas, a 1.6 cm enhancing lesion in the liver, and a 1.4 cm abdominal wall mass (Figure 2). A pituitary MRI was unremarkable. Given her suggestive history, genetic testing had been undertaken and was positive for MEN1. One copy of the pathogenic variant c.655-2A>C was noted in the MEN1 gene via sequencing.

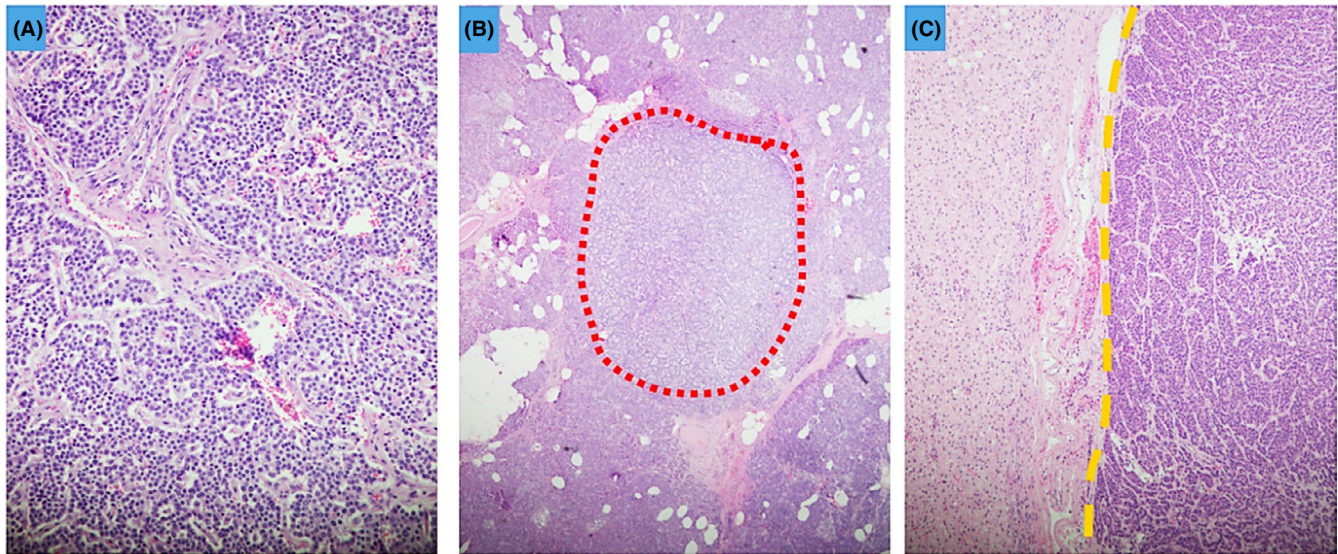
The patient subsequently underwent an exploratory laparotomy, partial hepatectomy, distal pancreatectomy, splenectomy, and resection of a duodenal mass. Intraoperative findings noted several pancreatic tail lesions which were visible grossly as well as by



**FIGURE 2** CT pancreas with contrast, showing hyper-enhancing liver lesion measuring 1.8 × 1.8 cm (red circle), pancreatic body lesion measuring 1.4 × 1.2 × 1.5 cm (red arrowhead) with central hypodense cystic area

palpation and ultrasound. There was no evidence of carcinomatosis.

The pancreas had multiple neuroendocrine tumors (NET), the largest measured 1.6 cm, and stained positive for insulin. Multiple neuroendocrine microadenomas (<0.5 cm for each nodule) were identified within the pancreas. The liver mass demonstrated a metastatic 1.8 cm well-differentiated NET but stained negative for insulin. Stains for chromogranin, synaptophysin, and cD56 were positive (Figure 3). The 1.7 cm duodenal mass was consistent with a leiomyoma. All surgical margins were negative, but focal lymphovascular and perineural invasion were identified within the pancreas with negative lymph nodes (0/27). She was diagnosed with a metastatic insulinoma with histopathology revealing a well-differentiated



**FIGURE 3** (A) Well-differentiated pancreatic neuroendocrine tumor; (B) Separate neuroendocrine microadenoma surrounded by normal pancreas; (C) Liver with metastatic well-differentiated neuroendocrine tumor (left side: normal liver; right side: metastatic tumor)

neuroendocrine tumor G1, <1mitosis/2mm<sup>2</sup>, Ki-67 <3%, stage pT1N0M1. Hypoglycemia resolved post-operatively.

#### 4 | OUTCOME AND FOLLOW-UP

At last short-term follow-up, 6 months after surgical resection, the patient continued to monitor her sugar daily via CGM. Interrogation of CGM revealed rare glucose readings into the 60 mg/dl range overnight as well as occasional postprandial excursions <180 mg/dl. She was able to lose the 7.5 kg of weight regain. Chromogranin A level normalized at 67 ng/ml (0–103) and post-operative A1c was slightly above target at 5.7%.

She was started on cinacalcet 15 mg daily for management of her recurrent primary hyperparathyroidism and referred to genetic counseling for her MEN1 diagnosis. Ongoing dietary modification for management of her glucose readings was encouraged. Follow-up CT imaging of the pancreas revealed post-surgical changes without suspicious enhancement at the surgical bed. However, a 5 mm focal enhancement within the residual body of the pancreas was noted, of unclear significance. This lesion, as well as any signs or symptoms of recurrent hypoglycemia, continues to be closely monitored.

#### 5 | DISCUSSION

This is a highly unusual presentation of metastatic insulinoma presenting after bariatric surgery. On review of medical literature, 8 cases of insulinoma post-bariatric surgery have been reported.<sup>3</sup> This is the second reported

case of metastatic insulinoma presenting after bariatric surgery, the first being in abstract form.<sup>2</sup>

The differential diagnosis for hypoglycemia is broad but in the seemingly well patient such as ours, it should include insulinoma, post-bariatric hypoglycemia, NIPHS, insulin autoimmune hypoglycemia, medications, and factitious hypoglycemia.<sup>4</sup> Given the patient's history of sleeve gastrectomy, post-bariatric hypoglycemia was a consideration. Although rare, postprandial hyperinsulinemic hypoglycemia can occur with both gastric bypass and sleeve gastrectomy.<sup>5</sup> The prevalence of postprandial hyperinsulinemic hypoglycemia after bariatric surgery is estimated to be 0.2%–0.36%, with most patients presenting within 1–2 years after surgery.<sup>5,6</sup> Autonomic or neuroglycopenic symptoms consistent with hypoglycemia are mostly postprandial occurring 1–3 h after a meal. This has been attributed to an increased level of incretins, increased beta cell sensitivity to GLP-1, and inappropriate hypersecretion of insulin.<sup>5</sup>

It is estimated that the incidence of insulinomas is about 4 per million each year.<sup>1</sup> About 10% of insulinomas are malignant with malignancy determined by presence of metastasis.<sup>7,8</sup> Estimations of the incidence of malignant insulinomas have been up to 0.27 cases/million person years over the last five decades.<sup>9</sup> It has been reported that at least 21% of patients with insulinoma present with both postprandial and fasting hypoglycemic symptoms while 6% have solely postprandial symptoms thus making the diagnosis of insulinomas simply by symptoms difficult.<sup>10</sup> As in our patient, when there is suspicion for endogenous hyperinsulinemia as the cause of hypoglycemic symptoms, a 72 h fast is necessary and the use of imaging to assess for insulinoma essential.<sup>11,12</sup> Although insulinomas

and NIPHS can both cause postprandial hypoglycemia, if MRI or CT is negative for a focal mass, endoscopic ultrasound to rule out a pancreatic mass, selective arterial calcium stimulation or DOTATATE PET/CT can help delineate between the two.

As observed in our patient, it is imperative that hypoglycemia predominantly in the fasting state, worsening shortly after bariatric surgery, refractory to dietary or medical management, or associated with weight regain or poor weight loss after bariatric surgery should be further evaluated to exclude insulinoma. Multiple case reports of insulinomas presenting after bariatric surgery have been reported in the literature.<sup>10,13–15</sup> A recent case report and review proposed an algorithm for evaluation of patients presenting with hypoglycemic symptoms after bariatric surgery, it emphasized the importance of timing of onset of symptoms after surgery and relation of symptoms to food intake.<sup>3</sup> Ours appears to be the second report of metastatic insulinoma diagnosed after bariatric surgery described in the literature.

Of importance, in this patient, concomitant evaluation resulted in a diagnosis of MEN1. MEN1 is a heritable disorder classically characterized by the occurrence of parathyroid, anterior pituitary, and pancreatic islet cell tumors. The clinical spectrum can also include gastrinomas, carcinoid tumors, adrenal tumors, lipomas, angiofibromas, and collagenomas. Insulinoma is associated with MEN1 in 10% of cases, and these particular tumors are often small and multiple as in our patient and can also be linked with other islet cell tumors.<sup>1,16</sup> It is conceivable that our patient's prior history of type 2 DM might have masked her symptoms; however, case reports of patients presenting with DM and insulinomas have been described with new-onset recurrent hypoglycemia not attributable to diabetic medications.<sup>17–20</sup>

The main treatment for insulinomas is surgery when possible but medical therapies are available when surgery is inappropriate or ineffective. Benign insulinomas carry an excellent prognosis after surgical resection.<sup>1</sup> Prognosis is worse for metastatic insulinomas with median overall survival estimated to be 143 months and a 55% 10-year overall survival.<sup>9</sup> Surgical resection is associated with increased survival, one study reported increased 5-year overall survival in the surgical group of 84% compared to 15% in the non-surgical group.<sup>9</sup>

Unlike with sporadic insulinoma cases, there is a higher rate of recurrence with MEN1-associated insulinomas reportedly 20% vs. 5%–7% without MEN1 over 20 years.<sup>1</sup> Thus, post-operative surveillance becomes even more critical in patients such as ours. Unfortunately, despite resolution of her symptoms, mild hypoglycemic episodes have recurred 6 months post-operatively and she is currently being managed medically. There are guidelines

explicitly giving guidance on the post-operative surveillance of insulinoma patients.<sup>7</sup> Per guidelines, patients require follow-up with imaging at 3–6 months after resection and then annually for at least 7 years.<sup>21</sup> It is unclear whether the post-bariatric surgery hormonal milieu can also contribute to the unmasking of insulinomas as has been suggested by Mulla et al.<sup>3</sup> Given the rare occurrence of post-bariatric surgery insulinomas, it will take further studies to elucidate if there are any contributing factors from the effects of the surgery.

## 6 | CONCLUSION

Hypoglycemia predominantly in the fasting state, worsening shortly after bariatric surgery, or refractory to dietary or medical management should be further evaluated to exclude insulinoma. Given this patient's suggestive medical history, there was a concern for MEN1, thus prompting genetic testing. Unlike with sporadic cases, there is a higher rate of recurrence with MEN1-associated insulinoma. Metastatic insulinoma remains a rare disease. Surgical resection should be completed, when possible, to improve patient survival. MEN1 must always be considered as an etiology in the evaluation of insulinoma since it impacts follow-up and management.

## ACKNOWLEDGEMENTS

None.

## CONFLICTS OF INTERESTS

None.

## AUTHOR CONTRIBUTION

Caroline Poku, MD prepared the discussion and literature review. Hafsa Amjed, MD was involved in the case presentation. Fatima Kazi, MD was involved in abstract and key clinical message. Shanika Samarasinghe, MD was involved in revision.

## ETHICAL APPROVAL

The manuscript in part or in full has not been submitted or published anywhere. The case was submitted as an abstract to the Endocrine Society annual meeting in 2021.

## CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

## DATA AVAILABILITY STATEMENT

Not applicable.

## ORCID

Caroline Poku  <https://orcid.org/0000-0001-8850-8949>

## REFERENCES

- Service FJ, McMAHON MM, O'Brien PC, Ballard DJ. Functioning insulinoma-incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clin Proc.* 1991;66(7):711-719. doi:10.1016/S0025-6196(12)62083-7
- Wehbeh L, Chen Cardenas S, Ganji S, Borzick D, Lee C, Sidhaye A. SUN-LB058 metastatic insulinoma after bariatric surgery. A diagnostic challenge. *J Endocr Soc.* 2019;3(Supplement\_1). doi:10.1210/js.2019-sun-lb058
- Mulla CM, Storino A, Yee EU, et al. Insulinoma after bariatric surgery: diagnostic dilemma and therapeutic approaches. *Obes Surg.* 2016;26(4):874-881. doi:10.1007/s11695-016-2092-5
- Kittah NE, Vella A. Pathogenesis and management of hypoglycemia. *Eur J Endocrinol.* 2017;177(1):R37-R47. doi:10.1530/EJE-16-1062
- Eisenberg D, Azagury DE, Ghiassi S, Grover BT, Kim JJ. ASMBS position statement on postprandial hyperinsulinemic hypoglycemia after bariatric surgery. *Surg Obes Relat Dis.* 2017;13(3):371-378. doi:10.1016/j.soard.2016.12.005
- Marsk R, Jonas E, Rasmussen F, Näslund E. Nationwide cohort study of post-gastric bypass hypoglycaemia including 5,040 patients undergoing surgery for obesity in 1986–2006 in Sweden. *Diabetologia.* 2010;53(11):2307-2311. doi:10.1007/s00125-010-1798-5
- Baudin E, Caron P, Lombard-Bohas C, et al. Malignant insulinoma: recommendations for characterisation and treatment. *Ann Endocrinol (Paris).* 2013;74(5–6):523-533. doi:10.1016/j.ando.2013.07.001
- Hirshberg B, Cochran C, Skarulis MC, et al. Malignant insulinoma: spectrum of unusual clinical features. *Cancer.* 2005;104(2):264-272. doi:10.1002/cncr.21179
- Sada A, Glasgow AE, Vella A, Thompson GB, McKenzie TJ, Habermann EB. Malignant insulinoma: a rare form of neuroendocrine tumor. *World J Surg.* 2020;44(7):2288-2294. doi:10.1007/s00268-020-05445-x
- Placzkowski KA, Vella A, Thompson GB, et al. Secular trends in the presentation and management of functioning insulinoma at the mayo clinic, 1987–2007. *J Clin Endocrinol Metab.* 2009;94(4):1069-1073. doi:10.1210/jc.2008-2031
- Service FJ. Diagnostic approach to adults with hypoglycemic disorders. *Endocrinol Metab Clin North Am.* 1999;28(3):519-532. doi:10.1016/S0889-8529(05)70086-4
- Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2009;94(3):709-728. doi:10.1210/jc.2008-1410
- Duff JM, Ghayee HK, Weber M, Thomas RM. Delayed imaging presentation of a symptomatic insulinoma after bariatric surgery. *J Gastrointest Surg.* 2017;21(2):412-414. doi:10.1007/s11660-016-3219-7
- Edwards K, de La Portilla L, Mirza FS, Luthra P. Proinsulin-predominant pancreatic neuroendocrine tumor-induced hypoglycemia after ROUX-EN-Y gastric bypass surgery. *AACE Clin Case Rep.* 2019;5(6):e339-e343. doi:10.4158/ACCR-2019-0148
- Zagury L, Moreira RO, Guedes EP, Coutinho WF, Appolinario JC. Insulinoma misdiagnosed as dumping syndrome after bariatric surgery. *Obes Surg.* 2004;14(1):120-123. doi:10.1381/096089204772787419
- Brandi ML, Gagel RF, Angeli A, et al. Consensus: guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab.* 2001;86(12):5658-5671. doi:10.1210/jcem.86.12.8070
- Ouleghzal H, Ziadi T, Menfaa M, Safi S. Association of insulinoma and type 2 diabetes mellitus. *Int J Endocrinol Metab.* 2017;15(1):39439. doi:10.5812/ijem.39439
- Cander S, Gül ÖÖ, Yildirim N, Ünal OK, Saraydaroglu Ö, Imamoğlu Ş. A rare cause of hypoglycemia in a type 2 diabetic patient: insulinoma. *J Diabetes Complications.* 2012;26(1):65-67. doi:10.1016/j.jdiacomp.2011.12.003
- Filippella M, Davi MV, Doveri G, et al. Hyperinsulinemic hypoglycemia associated with ectopic Cushing's syndrome due to a pancreatic endocrine tumor in a type 2 diabetes mellitus patient: clinical implications of a rare association. *J Endocrinol Invest.* 2011;34(3):175-179. doi:10.3275/6975
- Lei WY, Wang TE, Chen TL, Chang WH, Yang TL, Wang CY. Insulinoma causing hypoglycemia in a patient with type 2 diabetes. *J Formos Med Assoc.* 2007;106(5):392-396. doi:10.1016/S0929-6646(09)60324-7
- Kunz PL, Reidy-Lagunes D, Anthony LB, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas.* 2013;42(4):557-577. doi:10.1097/MPA.0b013e31828e34a4

**How to cite this article:** Poku C, Amjed H, Kazi F, Samarasinghe S. Metastatic insulinoma presenting after bariatric surgery in a patient diagnosed with MEN1. *Clin Case Rep.* 2022;10:e05419. doi:[10.1002/ccr3.5419](https://doi.org/10.1002/ccr3.5419)