The approach to symptomatic hypoglycemia in a non-diabetic patient

Concerning a case with a solid pancreatic lesion

Camila Andrea Guerrero-Bermúdez, Laura María Oliveros-Riveros, Valentina Vargas-Ramírez, Emmanuel Fernández-Garcés, Gabriel Mosquera-Klinger • Medellín (Colombia)

DOI: https://doi.org/10.36104/amc.2024.3007

Abstract

Tumor-mediated hypoglycemia is a rare phenomenon that warrants a comprehensive approach, in which an accurate diagnosis must be established to determine which interventions to employ. Insulinomas are the tumors that most often cause hypoglycemia. However, a variety of both solid and hematological malignancies can cause paraneoplastic hypoglycemia through different pathophysiological mechanisms. We present the clinical case of a patient with symptomatic hypoglycemia in the context of advanced solid organ malignancy. A comprehensive approach was used to ascertain the exact cause of the hypoglycemia and, consequently, determine its treatment and prognosis. **(Acta Med Colomb 2024; 49. DOI: https://doi.org/10.36104/amc.2024.3007).**

Keywords: *hypoglycemia, insulinoma, pancreatic cancer, prostate cancer, differential diagnosis*.

Dra. Camila Andrea Guerrero-Bermúdez: Sección de Medicina Interna, Universidad de Antioquia; Dres: Laura María Oliveros-Riveros, Valentina Vargas-Ramírez, Emmanuel Fernández-Garcés: Facultad de Medicina, Universidad EIA;
Dr. Gabriel Mosquera-Klinger: Unidad de Gastroenterología y Endoscopia Digestiva, Hospital Pablo Tobón Uribe. Medellín (Colombia).
Correspondencia: Gabriel Mosquera-Klinger. Medellín (Colombia).
E-mail: gami8203@yahoo.com
Received: 31/VII/2023 Accepted: 18/I/2024

Introduction

Hypoglycemia in non-diabetic patients outside of the critical care setting is rare (1, 2). The proper strategy requires a sequential approach to evaluate all the potential differential diagnoses. Hypoglycemia in a patient with advanced cancer should make us think, first of all, of a paraneoplastic phenomenon. However, other differential diagnoses of interest should be considered.

In this article, we present the case of a patient with advanced prostate cancer who consulted due to episodes of symptomatic hypoglycemia, with imaging evidence of a solid pancreatic lesion, in whom the initial comprehensive and sequential approach helped establish the diagnosis of insuloma-related hypoglycemia, and thus definitive treatment.

Clinical case

We present the case of a man in his sixties with a history of stage IV prostate cancer with vertebral metastases, who was treated with a transurethral resection of the prostate, bilateral orchidectomy and hormone therapy with degarelix, achieving a favorable biochemical response. He presented to the emergency room one year after his prostate cancer diagnosis complaining of frequent episodes of dizziness, diaphoresis and seizures, which improved with food intake. Initially, the symptoms were confirmed to be secondary to hypoglycemia, due to their temporal relationship with blood sugar levels below 54 mg/dL, and their resolution with glucose ingestion. Later, the medical history ruled out the surreptitious use of hypoglycemic medications, and he was therefore admitted to the hospital for a fasting test to classify the type of hypoglycemia.

In the beginning, the results of the fasting test suggested a non-hyperinsulinemic hypoglycemia (Table 1), which led to a suspicion of paraneoplastic hypoglycemia associated with his prostate cancer.

At the same time, an abdominal tomography reported a 16 mm nodular lesion in the head of the pancreas (Figure 1A). Due to this finding and the fact that pancreatic insulinomas are the main cause of tumoral hypoglycemia, a potential lab error was suggested, and the fasting test was repeated to confirm the results. On this occasion, ketone bodies were also measured, along with insulin-like growth factor (IGF-II) and insulin-like growth factor binding protein-3 (IGFBP-3), whose values are presented in Table 1.

On the second fasting test, the results indicated hyperinsulinemic hypoglycemia (high insulin, low ketone bodies) and the IGF II and IGFBP-3 levels were within normal limits, which supports the diagnosis of a pancreatic insulinoma and substantially reduces the possibility of non-hyperinsulinemic paraneoplastic hypoglycemia related to the prostate cancer.

Due to the diagnostic questions, the patient underwent a biopsy of the pancreatic lesion guided by endoscopic ultrasound (EUS), for diagnostic and therapeutic purposes. The result of this biopsy confirmed the presence of a well-differentiated grade 1/3 neuroendocrine tumor (with a Ki-67

Table 1. *Laboratory results (for the fasting test) during hospitalization.*

Test	Central glycemia (RV 70-100 mg/dL)	Insulin (RV 2.7-10.4 uU/mL)	C-peptide (RV 0.48-5.05 ng/ml)	IGF-II (RV 267-616 ng/mL)	IGFBP-3 (RV 3-6.2 mcg/mL)
First fasting test	47 mg/dL	4.9 uU/mL	0. 68 ng/ml (RV 0.48-5.05)		
Second fasting test	27 mg/dL	22. 7 uU/mL	4.2 ng/ml	410 ng/ml (RV 267-616)	3.5 mcg/mL (RV 3-6.2)

**RV: reference value; IGF-II: Insulin-like growth factor; IGFBP-3: Insulin-like growth factor binding protein-3.*

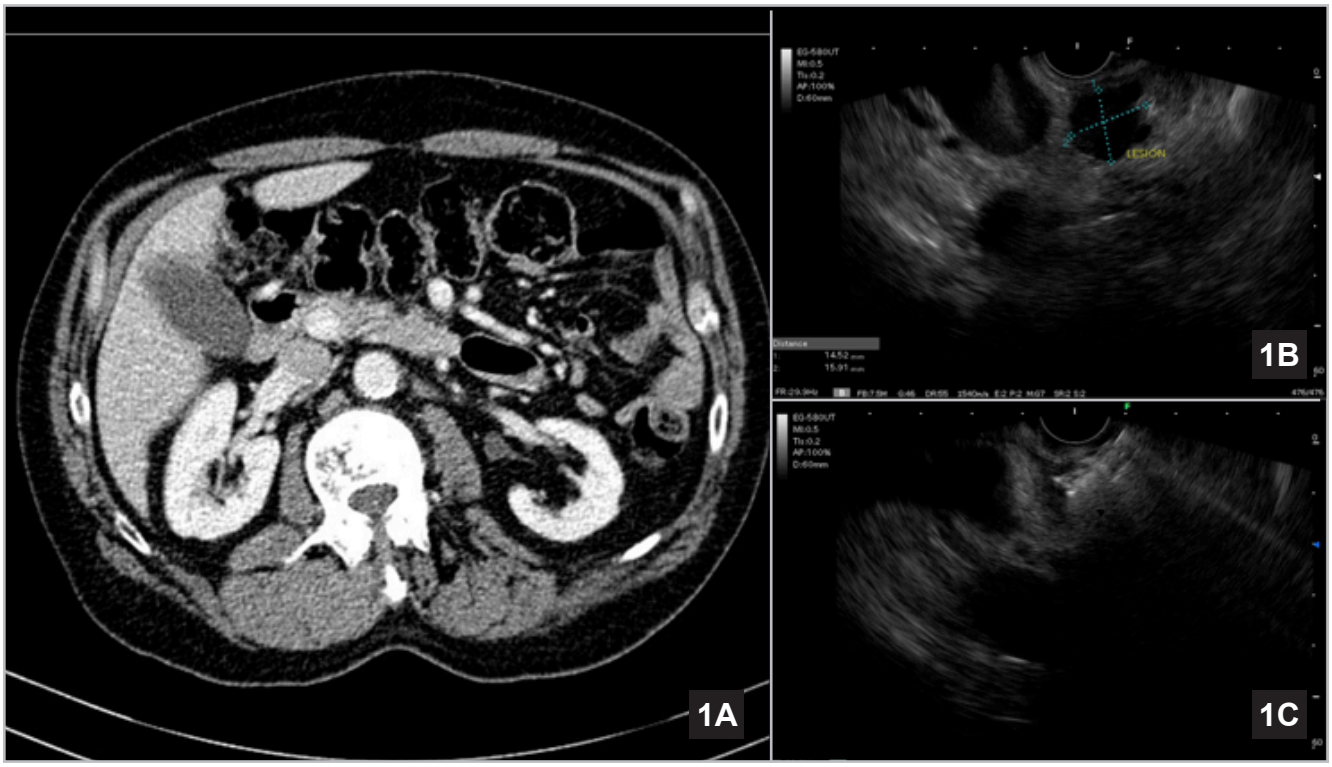

Figure 1. Abdominal CT. A. *Abdominal CT showing a nodular lesion in the head of the pancreas,* **B.** *Endoscopic ultrasound imaging: a homogenous, oval, hypoechoic image (lesion measurements),* **C.** *Endoscopic ultrasound image showing a hyperechoic area over the lesion (while performing 96% ethanol ablation)..*

index of 1% and a mitotic index of 1%) (Figure 1B). With these findings, in the context of advanced prostate cancer, surgical resection of the lesion was ruled out, opting instead for EUS-guided ethanol ablation of the tumor (Figure 1C). The ablation was successfully performed with complete symptom resolution and blood sugar normalization, which allowed the patient to be discharged the following day. Clinical follow up was done on-site one month after discharge, and by telephone every three months throughout the first year, with no symptom recurrence.

Discussion

The definition of insulinoma-related hypoglycemia was introduced by Whipple in 1938 (3). The classic description of the "Whipple" triad consists of the presence of signs and symptoms of hypoglycemia (4), and resolution of these symptoms with glucose ingestion. The presence of symptoms with normal glucose levels is secondary to other conditions, and isolated hypoglycemia is not diagnostic, either, as the glycemic thresholds for response may vary from person to person. However, a recurrent central blood glucose level less than 55 mg/dL should not be ignored (1).

Clinically, sympathetic autonomic nervous system symptoms tend to appear first (tremors, palpitations, anxiety, diaphoresis, hunger and paresthesia), but are non-specific. Neuroglycopenic symptoms like blurred vision, diplopia, dysarthria, seizures, confusion, loss of consciousness, coma and even death, while non-specific, are more related to actual hypoglycemia (1, 5). The symptoms tend to be similar from one episode to another and may occur both during fasting as well as after eating (6).

Hypoglycemia in non-diabetic patients is rare. In its latest guidelines on this subject (6), the American Association of Clinical Endocrinology mentioned that the first step in

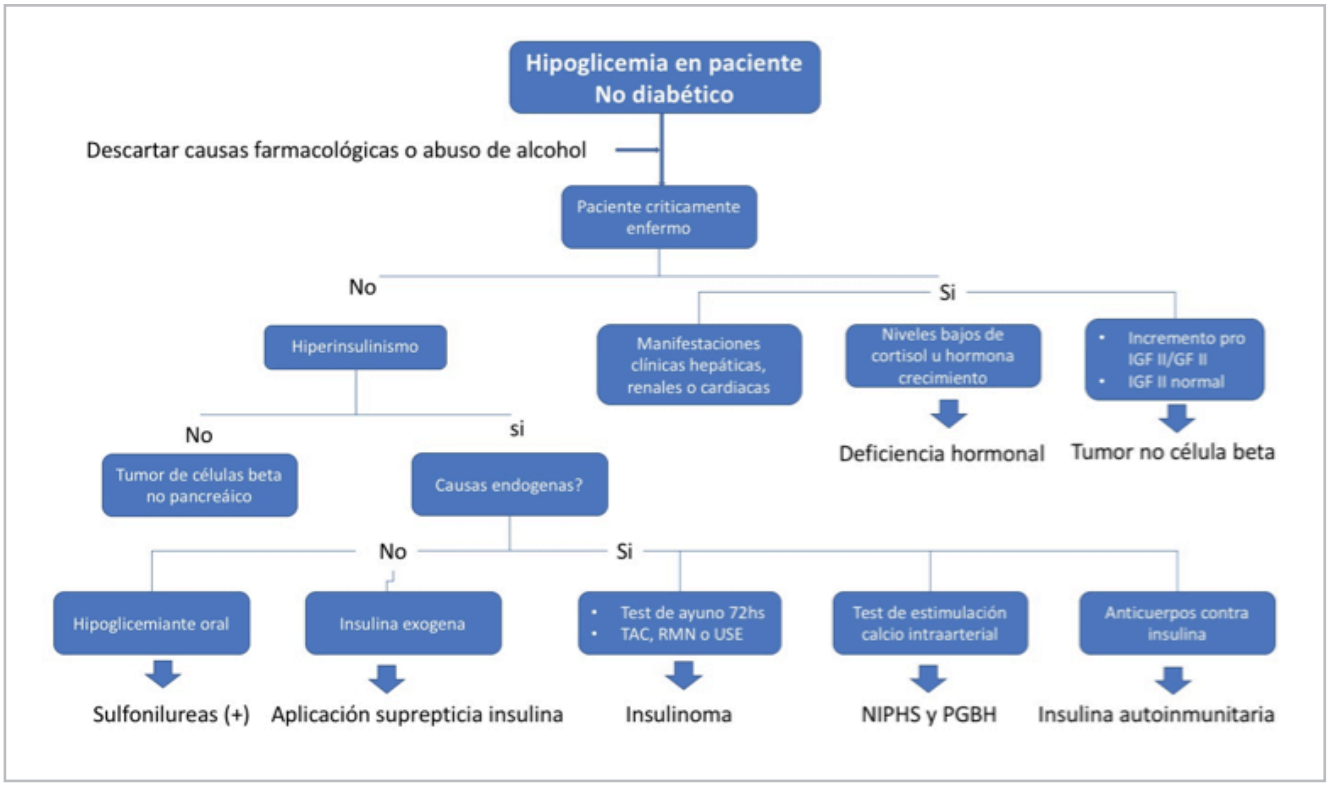

Figure 2. *Hypoglycemia algorithm in non-diabetic patients*.

evaluating this group of patients is to determine if the person is critically ill or is "apparently healthy" (Figure 2). Most hypoglycemic episodes in non-diabetic patients are related to critical illnesses (sepsis, multiple organ failure, hormone deficiencies) or multiple comorbidities. These are associated with increased in-hospital mortality (5, 6). In these cases, the medical history and physical exam are enough to establish the diagnosis.

On the other hand, outside of critical care, in "apparently healthy" patients, this is a very unusual event. This can be seen in a retrospective case series of 37,898 patients outside of the intensive care unit, which only found 71 episodes of hypoglycemia, most related to significant comorbidities or alcohol abuse, and only seven cases with no clear etiology (5).

After ruling out critical illness as the cause of hypoglycemia, the possibilities are reduced to surreptitious use of drugs like insulin or sulphonylureas; endogenous hyperinsulinism (tumoral or autoimmune); non-islet-cell tumors; or hypoglycemia following gastric bypass surgery, also known as dumping syndrome (1). At this point, laboratory tests are key for the definitive diagnosis. The fasting test is necessary to reproduce the hypoglycemia and run additional tests like levels of insulin, C-peptide (to diagnose hyperinsulinism) and ketone bodies, or IGF II and IGFBP-3 if a paraneoplastic syndrome not related to hyperinsulinism is suspected (7-9).

The fasting test has two goals: to confirm the diagnosis and determine the etiology of the hypoglycemia, according to the levels of glucose, insulin, C-peptide, proinsulin, and beta-hydroxybutyrate (BHB) and the blood glucose response after injecting 1 mg of glucagon. Interpretation is based on the physiology of insulin: if the insulin is high, this suggests a hyperinsulinemic origin (autoimmune, insulinoma), as in our case. Plasma C-peptide differentiates endogenous hyperinsulinemia (if it is high) from exogenous hyperinsulinemia (if it is low) (7, 8). Insulin has an antiketogenic effect, and therefore BHB will be lower if the hypoglycemia is insulin-mediated, and this test is particularly useful when the insulin and C-peptide levels are borderline (9). The plasma response to glucagon is preserved in hyperinsulinemic hypoglycemia because insulin promotes glycogen synthesis, but is reduced in non-hyperinsulinemic cases because the glycogen stores are exhausted. Table 2 shows the interpretation of these assays during the fasting test. Insulin has an antiketogenic effect and, therefore, BHB will be lower if the hypoglycemia is insulin-mediated; this test is especially useful when insulin and C-peptide are borderline (9).

In a patient with a history of cancer, hypoglycemia can occur as a paraneoplastic phenomenon. Various mechanisms have been described, which can be divided into insulin dependent and non-insulin dependent mechanisms (2). The first case includes hyperinsulinemia, as the most frequent cause, almost always secondary to a pancreatic insulinoma or, less

Table 2. *Interpretation of the laboratory assays during the fasting test.*

Insulin μU/mL	C-peptide nmol/L	Proinsulin pmol/L	Increased glucose after glucagon mg/dL	Diagnostic interpretation
<3	<0.2	<5	<25	Normal
>>3	<0.2	<5	>25	Exogenous insulin
≥3	≥0.2	≥5	>25	Insulinoma
≥3	≥0.2	≥5	>25	Oral hypoglycemic agent

commonly, due to neuroendocrine tumors in other locations with ectopic insulin secretion (10, 11). In the second case, prostate cancer has been associated with IGF-II-mediated paraneoplastic hypoglycemia (4).

Excessive IGF-II production is the most familiar mechanism within the paraneoplastic hypoglycemia group, (4). It is an insulin-like growth factor found mainly bound to proteins in the circulation (90%), the IGF binding proteins (IGFBPs), mainly sub-type 3 (IGFBP-3) (95%). Patients with paraneoplastic hypoglycemia have more IGF-II transcription, especially in the form of precursors (pro IGF-II or "big-IGF II"); this precursor does not bind to transport proteins, and therefore penetrates more easily in the tissues and is more biologically active, which is why it is responsible for the hypoglycemia (11). Pro IGF-II also reduces the synthesis of growth hormone, insulin, IGF-I and IGFBP. Blood levels of IGF-II may be normal or high, as the true culprit is pro-IGF-II, which is not measured with the usual laboratory techniques. It is treated with tumor resection, and the use of steroids has also been reported (10).

In the case we presented, an insulinoma was diagnosed based on the second fasting test and abdominal CT and EUS biopsy findings. Insulinomas are rare neuroendocrine tumors, with an incidence of 1 to 4 per million inhabitants per year (11). They are more frequent in females and are almost always benign (90-95%) and small, usually less than 2 cm in diameter, with only 8% being larger than 5 cm (12, 13).

Abdominal computerized tomography is the first-line imaging modality, and magnetic resonance imaging may be considered for difficult cases. These techniques lead to diagnosis in 80% of cases. If these axial images are normal, but there is a high clinical suspicion of an insulinoma, they should be complemented with EUS and biopsies, with which a sensitivity of up to 100% can be achieved (13). Since this tumor has a low proliferation rate, PET with 18-fluorodeoxyglucose is not effective, nor is PET with gallium; only PET with 68 Ga-NOTA-MAL-cys40-exendin-4 has been found to be useful. This technique uses a glucagon-like peptide (GLP-1), as most insulinomas have GLP-1 receptors (14, 15).

As far as treatment for pancreatic insulinomas, tumor resection is ideal, either with open or laparoscopic surgery. However, the use of minimally invasive methods like EUS has been growing lately. This method uses the expeditious anatomical relationship between the upper gastrointestinal tract and the pancreas, through which punctures and either thermal (radiofrequency) or chemical (ethanol) ablations can be performed. These techniques have been growing around the world, with international and local experiences showing a good performance and few associated complications (16-18).

Conclusion

Tumors have different hypoglycemia-producing mechanisms, whether through direct insulin production or the production of substances that lead to a persistent insulin-like action. Although insulinomas are the most frequent etiology, both insulin dependent and non-insulin dependent mechanisms should be considered in all patients with advanced cancer and hypoglycemia, using a sequential approach to provide the correct differential diagnosis in order to evaluate the etiology and make the best decisions regarding medical or surgical treatment.

The request to publish this case was evaluated by the research and ethics committee at Hospital Pablo Tobón Uribe.

References

1. **Martens P, Tits J.** Approach to the patient with spontaneous hypoglycemia. *European Journal of Internal Medicine*. 1 de junio de 2014;25(5):415-21.
2. **Groot JWB de, Rikhof B, Doorn J van, Bilo HJG, Alleman MA, Honkoop AH, et al.** Non-islet cell tumour-induced hypoglycaemia: a review of the literature including two new cases. *Endocrine-Related Cancer*. 2007;14(4):979-93.
3. **Whipple AO**. Surgical treatment of carcinoma of the ampullary region and head of the pancreas. *Am J Surg*. 1938 Apr 1;40(1):260–3.
4. **Sako A, Yasunaga H, Matsui H, Fushimi K, Hamasaki H, Katsuyama H, et al.** Hospitalization with hypoglycemia in patients without diabetes mellitus. *Medicine (Baltimore)*. 2017;96(25):e7271.
5. **Nirantharakumar K, Marshall T, Hodson J, Narendran P, Deeks J, Coleman JJ, et al.** Hypoglycemia in Non-Diabetic In-Patients: Clinical or Criminal? Sesti G, editor. *PLoS ONE*. 2012;7(7):e40384.
6. **Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, et al.** Evaluation and Management of Adult Hypoglycemic Disorders: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*. 2009;94(3):709-28.
7. **Service FJ, O'Brien PC, McMahon MM, Kao PC.** C-peptide during the prolonged fast in insulinoma. *The Journal of Clinical Endocrinology & Metabolism*. 1993;76(3):655-9.
8. **Service FJ, O'Brien PC.** Increasing Serum Betahydroxybutyrate Concentrations during the 72-Hour Fast: Evidence against Hyperinsulinemic Hypoglycemia. *The Journal of Clinical Endocrinology & Metabolism*. 2005;90(8):4555-8.
9. **Abdulhadi B, Anastasopoulou C, Lekprasert P.** Tumor-Induced Hypoglycemia: An Unusual Case Report and Review of Literature. *AACE Clin Case Rep*. 2020;7(1):80-3.
10. **Iglesias P, Díez JJ.** MANAGEMENT OF ENDOCRINE DISEASE: A clinical update on tumor-induced hypoglycemia. *European Journal of Endocrinology*. 2014;170(4):R147-57.
11. **Salazar R, Wiedenmann B, Rindi G, Ruszniewski P.** ENETS 2011 Consensus

Guidelines for the Management of Patients with Digestive Neuroendocrine Tumors: An Update. *Neuroendocrinology*. 2011;95(2):71-3.

12. **Giannis D, Moris D, Karachaliou GS, Tsilimigras DI, Karaolanis G, Papalampros A, et al.** Insulinomas: from diagnosis to treatment. A review of the literature. *J BUON* [Internet]. 2020 May [accedido 2022 Oct 7];25(3)
13. **Abboud B, Boujaoude J.** Occult sporadic insulinoma: Localization and surgical strategy. *World J Gastroenterol*. 7 de febrero de 2008;14(5):657-65.
14. **Antwi K, Fani M, Heye T, Nicolas G, Rottenburger C, Kaul F, et al.** Comparison of glucagon-like peptide-1 receptor (GLP-1R) PET/CT, SPECT/CT and 3T MRI for the localisation of occult insulinomas: evaluation of diagnostic accuracy in a prospective crossover imaging study. *Eur J Nucl Med Mol Imaging*. 2018;45(13):2318-27.
15. **Maggio I, Mollica V, Brighi N, Lamberti G, Manuzzi L, Ricci AD, et al.** The functioning side of the pancreas: a review on insulinomas. *J Endocrinol Invest*. 2020;43(2):139-48.
16. **El Sayed G, Frim L, Franklin J, McCrudden R, Gordon C, Al-Shamma S, et al.** Endoscopic ultrasound-guided ethanol and radiofrequency ablation of pancreatic insulinomas: a systematic literature review. *Therap Adv Gastroenterol* [Internet]. 2021 Nov 18 [cited 2022 Oct 7];14.
17. **Garg R, Mohammed A, Singh A, Harnegie MP, Rustagi T, Stevens T, et al.** EUS-guided radiofrequency and ethanol ablation for pancreatic neuroendocrine tumors: A systematic review and meta-analysis. *Endosc Ultrasound*. 2022;11:170-85.
18. **Mosquera-Klinger G, Gutierrez JJC.** Endoscopic ultrasound-guided ethanol ablation for the management of a symptomatic pancreatic insulinoma. *Revista Espanola de Enfermadades Digestivas (REED)*. 2021;113:48-52.