

Hypoglycemia in patient with pancreatic adenocarcinoma with suspected concomitant insulinoma: A case report

Hipoglucemia en paciente con adenocarcinoma pancreático con sospecha de insulinoma concomitante. Reporte de caso

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ABSTRACT

Introduction: The coexistence of insulinoma and pancreatic adenocarcinoma is an extremely rare condition, reported in only a few cases worldwide. It poses a diagnostic challenge because persistent hypoglycemia in pancreatic neoplasms may be underestimated or attributed to the patient's overall clinical condition. **Case presentation:** We report the case of a 58-year-old woman diagnosed with pancreatic adenocarcinoma, who initially presented with recurrent episodes of severe hypoglycemia. Biochemical evaluation revealed hypoglycemia associated with hyperinsulinemia and elevated C-peptide levels. Octreotide scintigraphy demonstrated uptake in the pancreas and liver, suggesting the presence of a functional neuroendocrine neoplasm. However, histopathological analysis identified only adenocarcinoma, without confirmation of a neuroendocrine tumor. Despite two lines of chemotherapy and symptomatic management with Octreotide, Diazoxide, and glucagon, the clinical course was unfavorable. The clinical presentation was consistent with endogenous hyperinsulinemic hypoglycemia, which raised suspicion of a probable insulinoma coexisting with pancreatic adenocarcinoma. **Discussion:** This scenario requires considering differential diagnoses, including paraneoplastic causes and other etiologies of hypoglycemia in oncology patients. The lack of histopathological confirmation represents a significant limitation. **Conclusion:** This case highlights the importance of not underestimating hypoglycemia in patients with pancreatic neoplasms and of considering endocrine etiologies when the clinical presentation is not fully explained by the primary tumor.

Keywords: Insulinoma; pancreatic adenocarcinoma; hypoglycemia; neuroendocrine tumor; case report.

RESUMEN

Introducción: La coexistencia de insulinoma y adenocarcinoma de páncreas es una condición rara, documentada en muy pocos casos a nivel mundial. Esta representa un desafío diagnóstico porque, en neoplasias pancreáticas, la hipoglucemia persistente puede subestimarse o atribuirse al estado clínico del paciente. **Caso clínico:** Se presenta el caso de una mujer de 58 años con diagnóstico de adenocarcinoma pancreático y episodios recurrentes de hipoglucemia severa. Los estudios bioquímicos evidenciaron hipoglucemia con hiperinsulinemia y elevación de péptido C. La gammagrafía con octreótide mostró captación en páncreas e hígado, sugestiva de una neoplasia neuroendocrina funcional. Sin embargo, las biopsias realizadas evidenciaron únicamente adenocarcinoma, sin confirmación histopatológica de tumor neuroendocrino. A pesar de dos líneas de quimioterapia y manejo sintomático con octreótide, diazóxido y glucagón, la evolución fue desfavorable. El cuadro clínico fue compatible con hipoglucemia hiperinsulinémica endógena, con sospecha de insulinoma en coexistencia con adenocarcinoma pancreático. **Discusión:** Este escenario obliga a considerar diagnósticos diferenciales, incluidas las causas paraneoplásicas u otras etiologías de hipoglucemia en pacientes oncológicos. La ausencia de confirmación histológica constituye una limitación relevante. **Conclusiones:** Este caso resalta la importancia de no subestimar la hipoglucemia en pacientes con neoplasias pancreáticas y de considerar causas endocrinas cuando el cuadro clínico no se explica únicamente por el tumor primario.

Palabras clave: insulinoma, adenocarcinoma de páncreas, hipoglucemia, tumor neuroendocrino, reporte de caso.

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1. Introduction

Insulinomas are rare pancreatic neuroendocrine neoplasms, with an estimated incidence of 1 to 3 cases per million inhabitants per year [1]. They are more common in women in the fifth decade of life; 90% occur in the pancreas, 90% are benign, 90% are solitary, and 90% measure less than 2 cm in diameter [2].

The five-year survival associated with this neoplasm ranges from 94.5% to 100% for benign insulinomas and from 24% to 66.8% for malignant insulinomas [3]. In some cases, Whipple's triad, characterized by hypoglycemia, neuroglycopenic symptoms, and resolution of symptoms after glucose intake, may suggest the diagnosis of insulinoma [4]. The concomitant occurrence of pancreatic adenocarcinoma and insulinoma is exceptionally rare, with only three cases documented in the literature to date [5–7].

The objective of this report is to describe the case of a patient with a history of pancreatic adenocarcinoma who presented with recurrent episodes of hypoglycemia and biochemical and imaging findings suggestive of endogenous hyperinsulinemic hypoglycemia, raising suspicion of insulinoma. In addition, we discuss the main differential diagnoses, the diagnostic limitations, particularly the absence of histopathological confirmation—and the clinical implications of this unusual presentation.

2. Case presentation

A 58-year-old woman with a history of hypertension and stage IV pancreatic adenocarcinoma, who received six cycles of first-line chemotherapy with Gemcitabine and Oxaliplatin, with no significant response.

From the onset of the disease, the patient experienced recurrent episodes of symptomatic hypoglycemia and required parenteral glucose replacement on multiple occasions. Due to a clinical course not entirely attributable to pancreatic adenocarcinoma, a biopsy of hepatic metastases was performed; however, histopathological analysis showed no evidence of malignancy.

Subsequently, follow-up positron emission tomography-computed tomography (PET-CT) showed tumor viability in the pancreatic head, with metastatic hepatic and nodal disease. Therefore, second-line chemotherapy with Fluorouracil, Irinotecan, Oxaliplatin, and Leucovorin (FOLFIRI) was initiated and the patient completed 11 cycles. A follow-up PET-CT performed in January 2023 reported a complete metabolic response.

Due to the persistence of symptomatic hypoglycemic episodes, the patient was evaluated by the Endocrinology Department. She had no history of diabetes mellitus and denied the use of insulin, oral antidiabetic agents, or any other medications that could explain the clinical presentation. Given the suspicion of endogenous hyperinsulinemic hypoglycemia, targeted biochemical studies were requested; results are presented in [Table 1](#).

Table 1. Biochemical laboratory findings obtained during the diagnostic workup for insulinoma

Test	Result	Reference range
Fasting Blood Glucose	37 mg/dL	70–100 mg/dL
Insulin	32 μ U/mL	5–25 μ U/mL
C-peptide	3.66 ng/mL	0.5–2.7 ng/mL
Insulin/C-peptide ratio	0.18 $\leq$ 1	Not established

μ U/mL: micro units per milliliter; ng/mL: nanograms per milliliter; mg/dL: milligrams per deciliter.

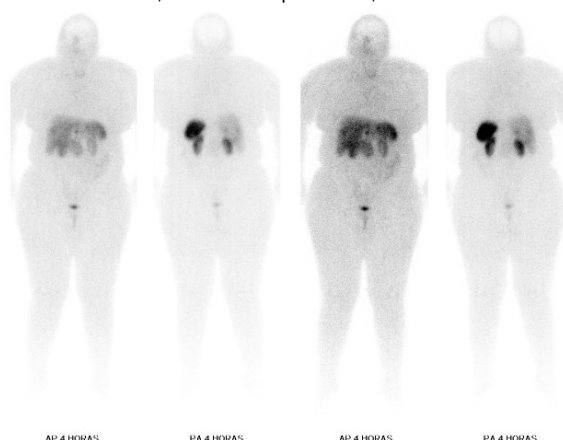
One month later, the patient was admitted to the emergency department with psychomotor agitation and emotional lability, with a documented blood glucose level of 30 mg/dL. Symptoms resolved after administration of 10% dextrose. A review of previous imaging studies led to an abdominal magnetic resonance imaging scan showing an irregular infiltrative pancreatic mass involving the head and uncinate process of the pancreas. It was associated with hepatic metastases and retroperitoneal lymphadenopathy ([Figure 1](#)). Given the suspicion of an underlying endocrine etiology, octreotide scintigraphy (Octreoscan) ([Figure 2](#)) was performed, and the liver lesion biopsy was repeated.

Figure 1. Abdominal MRI showing an irregular infiltrative pancreatic mass associated with hepatic metastases and retroperitoneal lymphadenopathy.



Source: SOLCA Guayaquil Imaging System.

Figure 2. Whole-body octreotide scintigraphy showing Krenning score 3 uptake in the pancreatic head, uncinate process, and liver.



Source: SOLCA Guayaquil Imaging System.

The liver biopsy revealed minimal fragments compatible with adenocarcinoma. Meanwhile, octreotide scintigraphy showed a heterogeneous mass involving the pancreatic head and uncinate process with peripheral radiotracer uptake (Krenning score 3), as well as multiple radiotracer-avid lesions in both hepatic lobes. Overall, the clinical, biochemical, and imaging findings were consistent with endogenous hyperinsulinemic hypoglycemia, thus raising suspicion of a probable insulinoma coexisting with pancreatic adenocarcinoma; however, there was no histopathological confirmation of a neuroendocrine tumor.

The case was discussed at a multidisciplinary gastrointestinal tumor board. Considering the presence of advanced metastatic disease and suspicion of an associated functional neoplasm, surgical intervention was not considered beneficial. Pharmacological management of hypoglycemic episodes with corticosteroids, Diazoxide, glucagon, and Octreotide was initiated with poor clinical response.

During hospitalization, the patient developed urinary sepsis and required management in the Intensive Care Unit, with unfavorable progression and death three weeks after admission.

To facilitate interpretation of the clinical course, a timeline summarizing the main diagnostic and therapeutic milestones, together with the occurrence of hypoglycemic episodes, is presented in [Table 2](#).

Table 2. Timeline of clinical, diagnostic, and therapeutic findings.

Date	Clinical event
August 2021	Onset of hypoglycemic episodes.
September 2021	Abdominal MRI: mass in the pancreatic head and uncinate process with hepatic metastases.
October 2021	Histopathology: moderately differentiated pancreatic adenocarcinoma.
November 2021 – June 2022	First-line chemotherapy (Gemcitabine + Oxaliplatin, 6 cycles).
April 2022	Liver biopsy: no evidence of malignancy.
July 2022	PET-CT: metastatic hepatic and nodal disease.
October 2022	Initiation of second-line therapy (FOLFIRI, 11 cycles).
2021–2023	Persistent recurrent hypoglycemia.
January 2023	PET-CT: complete metabolic response.
March 2023	Abdominal MRI: persistent tumor activity.
June 2023	Gastrointestinal tumor board: suspicion of functional endocrine neoplasm.
July 2023	Admission due to refractory hypoglycemia.
July 2023	Octreoscan: pancreatic and hepatic uptake (Krenning score 3).
Final outcome	Medical management: urinary sepsis, admission into ICU, and death.

MRI: magnetic resonance imaging. PET-CT: positron emission tomography-computed tomography.

3. Discussion

The coexistence of pancreatic adenocarcinoma and insulinoma is rare and poses significant diagnostic and therapeutic challenges. In this case, the presence of persistent hypoglycemia in a patient with pancreatic neoplasia raised the question of whether the clinical picture could be explained solely by adenocarcinoma or whether a second associated functional entity was present. Likewise, it was uncertain whether the biochemical profile and octreotide functional imaging studies were sufficient to support this diagnosis in the absence of histopathological confirmation.

Definitive diagnosis of malignant insulinoma requires histopathological evidence of vascular invasion, perineural invasion, or distant metastases [8]. In this case, both the liver biopsy and pancreatic tissue samples showed adenocarcinoma fragments without neuroendocrine features. This leaves open the possibility of two distinct neoplasms—adenocarcinoma and functional insulinoma—a hypothesis supported by the rarity of neuroendocrine transformation in ductal adenocarcinomas and by the absence of mixed histological characteristics [9,10].

From a diagnostic standpoint, although the biochemical profile combined with octreotide PET imaging provides high sensitivity for insulinoma detection, it does not confirm malignancy by itself [2,4,11]. A more precise diagnostic approach could have included gallium-68 DOTATATE positron emission tomography-computed tomography, which has greater sensitivity for well-differentiated neuroendocrine tumors, although this modality is not available at our facilities [12]. Targeted biopsy of hypercaptating lesions with immunohistochemical analysis, including chromogranin A and synaptophysin staining, might have allowed better characterization of tumor origin [13]. Similarly, measurement of proinsulin or IGF-II levels could have been useful in the context of refractory hypoglycemia, especially when other secreting tumors are suspected [14].

Hypoglycemia in patients with pancreatic neoplasms may result from different pathophysiological mechanisms, making it essential to distinguish between insulin-mediated and non-insulin-mediated causes. Endogenous hyperinsulinemic hypoglycemia (EHH) is defined by inappropriately elevated insulin levels in the setting of low plasma glucose and may be associated with several etiologies, including insulinoma, insulin autoimmune syndrome, and type B insulin resistance syndrome [15].

In this case, the biochemical profile obtained during hypoglycemic episodes showed elevated insulin and C-peptide levels, findings consistent with EHH. In contrast, paraneoplastic hypoglycemia is typically characterized by suppressed insulin and C-peptide levels due to the action of factors such as IGF-2. These findings support an insulin-mediated mechanism and reinforce suspicion of an underlying endocrine etiology rather than a paraneoplastic phenomenon [16,17].

The possibility of mixed pancreatic neoplasms, such as mixed acinar-neuroendocrine carcinoma of the pancreas (MANEC-P), should also be considered. These tumors are characterized by the coexistence of exocrine and neuroendocrine components within the same neoplasm, potentially explaining both hypoglycemia and repeated biopsies compatible with adenocarcinoma. However, these entities are uncommon, and their diagnosis requires a histological demonstration of both components [18,19].

In the present case, the analyzed tissue samples demonstrated only features compatible with adenocarcinoma, without expression of neuroendocrine markers or evidence of mixed differentiation. Although this possibility cannot be completely ruled out due to limitations in tissue sampling, the available findings make the hypothesis of a coexisting functional entity without histopathological confirmation more likely.

Regarding therapeutic management, given the unresectable metastatic disease, medical treatment of hypoglycemia with corticosteroids, Diazoxide, glucagon, and Octreotide was initiated [20]. In the context of functioning malignant insulinoma, other options such as Everolimus might have been considered, which is approved for pancreatic neuroendocrine tumors and may provide both antitumor and glycemic control benefits [21–23]. In addition, chemotherapy regimens based on Streptozocin combined with 5-fluorouracil or Doxorubicin have shown efficacy in advanced cases [24,25]. Finally, locoregional therapies such as hepatic ablation or selective embolization represent viable palliative alternatives in patients with severe hypoglycemia caused by functioning metastases [2,14].

Management of the possible coexistence of these neoplasms requires a multidisciplinary approach. Whereas insulinoma may often be treated surgically, adenocarcinoma may require surgery, chemotherapy, and/or radiotherapy depending on disease stage [5–8]. Prioritizing the most aggressive tumor is essential, while considering patient comorbidities and quality of life. Prognosis in patients with both neoplasms is generally poor because of the aggressive nature of pancreatic adenocarcinoma.

This case demonstrates that persistent hypoglycemia in patients with pancreatic neoplasms cannot always be attributed to the expected course of the disease. As occurred in our patient, this finding should prompt further targeted evaluation, as it may reflect an additional pathophysiological mechanism that, if overlooked, could delay diagnosis and limit management options.

When conclusive histopathological confirmation cannot be obtained, clinical reasoning and integration of biochemical and imaging findings become central to diagnosis. This type of presentation highlights the need to continue exploring diagnostic strategies that allow better characterization of these conditions, particularly in patients with complex oncologic conditions.

4. Conclusion

The coexistence of pancreatic adenocarcinoma and a clinical picture compatible with endogenous hyperinsulinemic hypoglycemia is uncommon and poses significant diagnostic challenges. In this case, the presence of persistent hypoglycemia prompted consideration of an additional endocrine etiology, even in the absence of histopathological confirmation. This scenario highlights the importance of maintaining a comprehensive diagnostic approach in patients with pancreatic neoplasms and clinical manifestations not fully explained by the primary tumor.

5. Abbreviations

EHH: Endogenous Hyperinsulinemic Hypoglycemia

FOLFIRI: Folinic acid, fluorouracil and irinotecan

Ga-68 DOTATATE: Gallium-68 DOTA-octreotate

ICU: Intensive Care Unit

IGF-2: Insulin-like growth factor 2

MANEC-P: Mixed AdenoNeuroEndocrine Carcinoma of the Pancreas

PET-CT: Positron Emission Tomography combined with Computed Tomography

6. Administrative information

6.1 Additional files

Signed informed consent from the patient and a family member authorizing publication of the case and relevant medical images, while guaranteeing anonymity and confidentiality, has been submitted to the journal.

6.2 Acknowledgments

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6.3 Author contributions

Karla Nicole Aguirre Ordóñez: Investigation, Conceptualization, Writing – Original Draft, Formal Analysis.

Noemi Bautista Litardo: Supervision, Writing – Review & Editing.

6.4 Funding

None.

7. Declarations

7.1 Consent for publication

Written informed consent was obtained from the patient and her family members for publication of this clinical case, including relevant clinical data and diagnostic images. They were informed that no identifying information would be disclosed and that the material would be used exclusively for academic and scientific purposes. Compliance with the ethical principles and confidentiality standards established by the Declaration of Helsinki and applicable institutional regulations was guaranteed.

7.2 Conflicts of interest

The authors declare no conflicts of interest.

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