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Case Report

Diagnosing Hypoglycemia–from Liver Cancer to Insulinoma: A Case Report

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Abstract

Insulinoma is a neuroendocrine tumor originating in the pancreas that secretes excess amounts of insulin, leading to severe hypoglycemia. The clinical presentation of hypoglycemia is classically described by Whipple's Triad. Due to the rarity of this diagnosis, it can often be mistaken for other etiologies with similar presentations. In this paper, we present the case of a woman in her 70s with metastatic insulinoma involving the liver, who was initially diagnosed with an insulin-like growth factor 2-secreting hepatocellular carcinoma. Biochemical and immunohistochemical analyses were instrumental in distinguishing between these two etiologies.

Introduction

Hypoglycemia as a complication of cancer can occur either due to excessive insulin secretion, as in insulinoma, or as non-islet cell tumor hypoglycemia (NICTH), a serious paraneoplastic syndrome in which tumors secrete elevated levels of insulin-like growth factor 2 (IGF-2).[1,2] Metastatic insulinoma is extremely rare. Among 121 cases of malignant insulinoma reported from 1973 to 2015 in the Surveillance, Epidemiology, and End Results registries, which cover approximately 34.6% of the United States population, 66 patients (54.4%) had metastatic insulinoma with regional or distant metastases.[3] NICTH is usually associated with large mesenchymal tumors, including hepatocellular carcinoma. This condition is also rare, and its exact incidence remains unknown.[4] Clinically, both conditions present similarly with Whipple Triad of hypoglycemia; therefore, diagnosis depends on objective methods. This case aimed to highlight an integrated diagnostic approach combining laboratory results, histopathology, and targeted imaging to determine the cause of hypoglycemia in a patient with liver lesions.

Case presentation

We present the case of a woman in her 70s with a history of hypertension and hyperlipidemia, a non-smoker with rare alcohol consumption, who was initially referred to our institution following a diagnosis of hepatocellular carcinoma (HCC) based on external pathology.

Two months prior to presentation, the patient visited her primary care physician complaining of mid-epigastric pain, reflux, and profuse sweating, symptoms that began shortly after receiving her second dose of the COVID-19 vaccine. An initial ultrasound revealed an 8 × 6.1 × 6.2 cm hyperechoic lesion in the right lobe of the liver, along with four smaller hyperechoic nodules scattered throughout the liver. A follow-up computed tomography (CT) scan of the abdomen and pelvis, performed with and without contrast, identified a noncirrhotic hepatic morphology with several hypodense lesions visible on non-contrast images. These lesions demonstrated arterial phase hyperenhancement exceeding that of the surrounding liver parenchyma, followed by peripheral washout in the portal venous phase (Fig. 1). These imaging features are classic for Liver Imaging Reporting and Data System category 5 lesions, consistent with HCC. Some lesions exhibited smooth, uniform borders suggestive of a capsule, which is typical for HCC. Additionally, the lesions were large (greater than 2 cm), supporting a higher likelihood of malignancy.

Two weeks later, the patient began experiencing episodes of disorientation and diaphoresis, which resulted in a fall. Emergency medical services were called, and laboratory testing revealed a blood glucose level of 32 mg/dL. She was admitted to a community hospital and diagnosed with a urinary tract infection and paroxysmal atrial fibrillation. However, despite treatment for the urinary tract infection, her blood glucose levels remained abnormally low without an obvious cause. A CT-guided liver biopsy demonstrated a moderately differentiated carcinoma with lymphovascular invasion, focally weakly positive alpha-fetoprotein (AFP), and nega-

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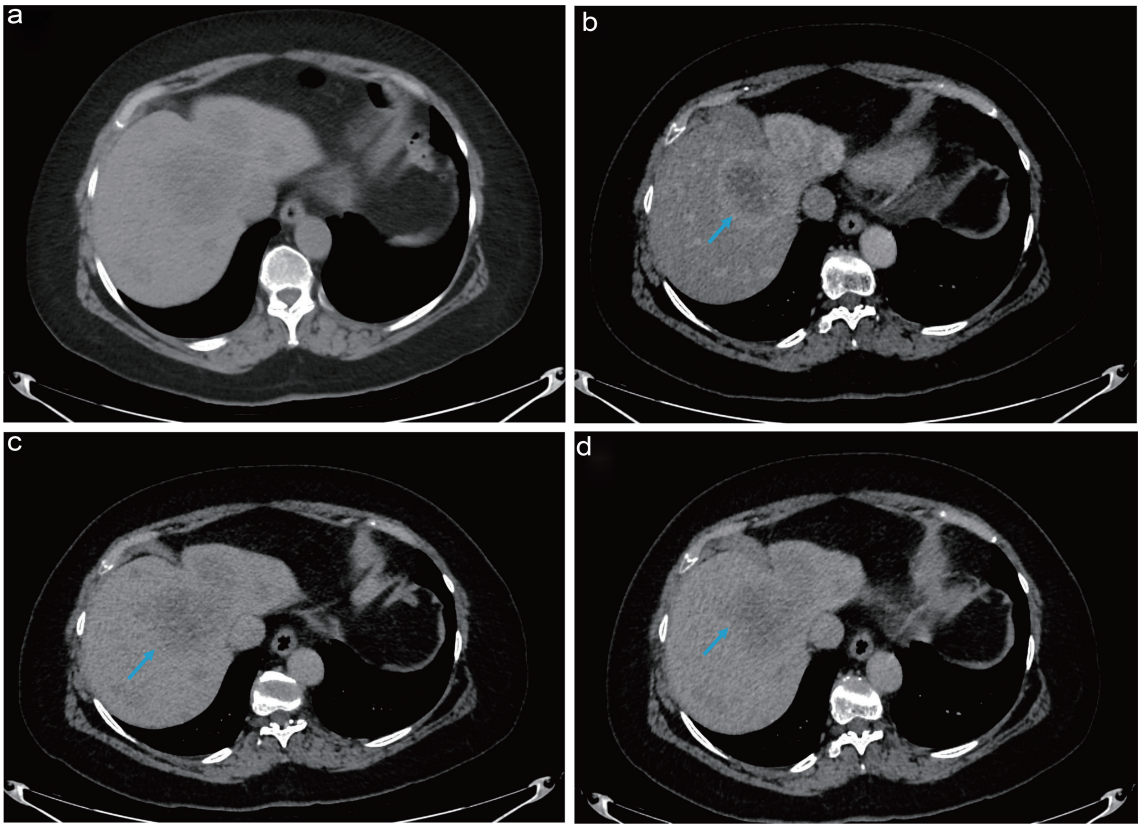

Fig. 1. Baseline CT imaging (a) non-contrast enhanced, and contrast enhanced- (b) arterial phase demonstrating hyperenhancement, (c) and (d) portal venous phase demonstrating washout. CT, computed tomography.

tive Glypican-3 staining. Based on these findings, she was diagnosed with HCC accompanied by hypoglycemia, likely secondary to increased secretion of IGF-2 from a non-islet cell tumor. A treatment plan was developed for interventional radiology–guided embolization of the left and middle hepatic veins.

During her hospital stay following embolization, the patient experienced persistent hypoglycemia, necessitating continuous dextrose infusion, along with diazoxide and a prolonged course of daily steroids. Additional laboratory tests were performed to investigate other potential causes of hypoglycemia, as outlined in Table 1.

These findings, combined with normal IGF-2 levels, indicated that the hypoglycemia was due to hyperinsulinemia rather than an IGF-2-mediated process. Initial CT imaging revealed multiple masses throughout both lobes of the liver, with the largest lesion centrally located in the right lobe, measuring approximately 6.2 cm. There was peripheral enhancement and central hypoenhancement that persisted on both early and delayed post-contrast images. This pattern is not entirely typical of any benign etiology. HCC appears on CT as a mass that enhances during the arterial phase and washes out in the portal or delayed venous phase.[5] However, because the patient did not have underlying cirrhosis or hepatitis, the Liver Imaging Reporting and Data System criteria could not be reliably applied.[6] Consequently, previous scans were reviewed,

Table 1. Trend of laboratory findings

	Reference values	Initial presentation (prior to any therapy)	After nine months of octreotide	After one month of everolimus
Glucose (mg/dL)	70–140	34 (↓)	121	122
Serum insulin (microU/mL)	0.0–17	91.9 (↑)	99.2 (↑)	41.7 (↑)
C-peptide (ng/mL)	0.69–2.45	11.06 (↑)	6.21 (↑)	6.38 (↑)
Proinsulin (pmol/L)	3.6–22	>700 (↑↑)	498 (↑↑)	–
Alpha fetoprotein (ng/mL)	0–5	3,542.8 (↑↑)	–	–
IGF 1 (mcg/mL)	34–187	153	–	–
IGF 2 (mcg/mL)	333–967	441	516	–

IGF, insulin-like growth factor. ↓, decrease; ↑, increase.

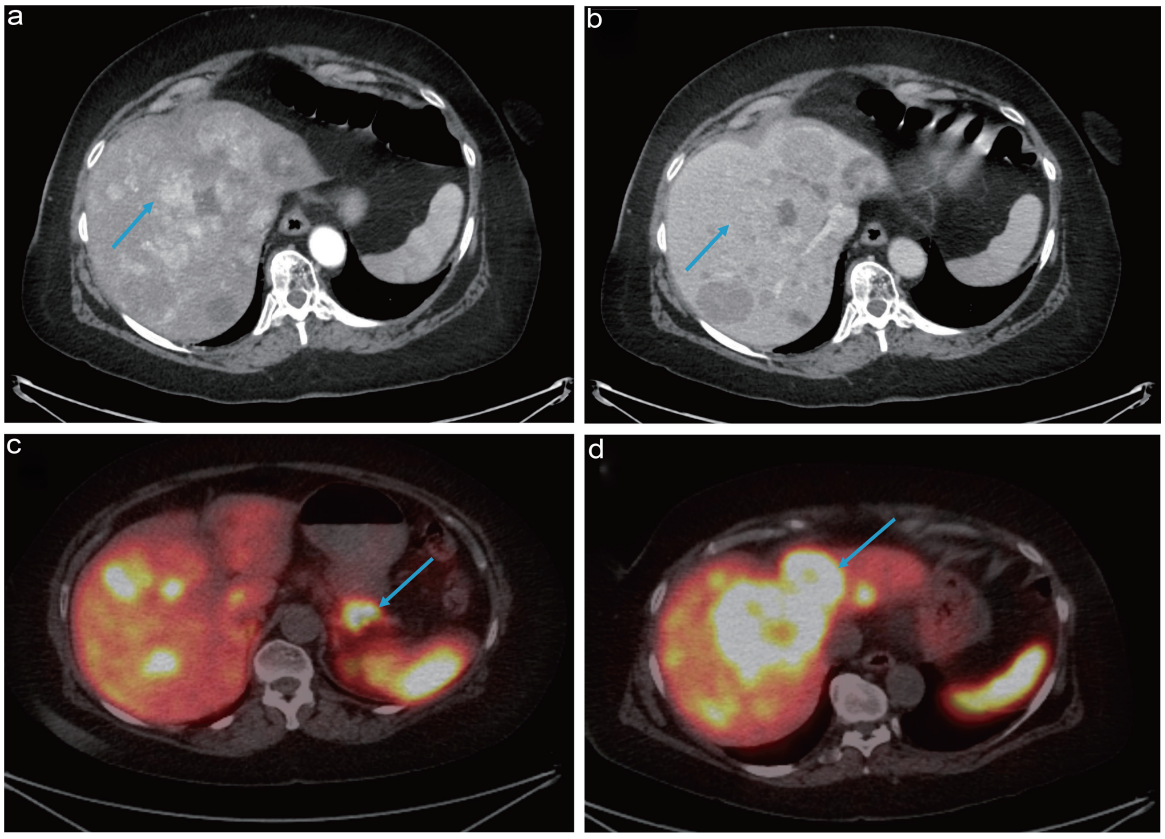

Fig. 2. Subsequent CT scan (a) contrast enhanced- arterial phase, (b) portal venous phase, PET scan (c) DOTATATE avid pancreatic lesion, (d) DOTATATE avid liver metastases. CT, computed tomography; PET, positron emission tomography.

and a triphasic CT scan of the liver was performed. This subsequent scan demonstrated an interval increase in lesion size, another feature favoring HCC (Fig. 2).

The scan also identified a sub-centimeter hypodense lesion with calcifications in the pancreatic tail. Given the suspicion of insulinoma, an esophagogastroduodenoscopy with endoscopic ultrasound and magnetic resonance cholangiopancreatography were performed but showed no definitive evidence of a pancreatic lesion. Consequently, a positron emission tomography DOTATATE (PET-DOTATATE) scan was scheduled to evaluate for a neuroendocrine tumor (NET). The result revealed intense somatostatin receptor-positive bilobar liver lesions, consistent with malignancy, as well as intense tracer avidity in the gastropancreatic region, likely misregistered from the pancreatic tail (Fig. 2). This finding raised suspicion for a primary neuroendocrine neoplasm, correlating with the calcification previously noted on CT.

A review of the earlier biopsy performed at our institution during this period led to a revised diagnosis of metastatic well-differentiated NET, consistent with a pancreatic primary. Additional immunostaining confirmed the tumor's neuroendocrine origin, with cells testing positive for synaptophysin and chromogranin and showing patchy insulin staining, while negative for HepPar-1, Arginase-1, trypsin, and chymotrypsin. The tumor exhibited a proliferation index (Ki-67) of approximately 25–30% (World Health Organization Grade 3) and a mitotic rate of approximately two to four per 10 high-power fields (Fig. 3). These findings reinforced the neuroendocrine origin of the tumor, distinguishing it from the initial diagnosis of HCC.

Following the revised diagnosis, the patient began monthly octreotide injections one month after her first embolization. Eight weeks later, she underwent a second embolization. Over the subsequent seven months, her blood glucose levels remained well-controlled, allowing her to wean off both steroids and diazoxide. Fingerstick glucose monitoring served as a practical and cost-effective alternative to more expensive tests, such as insulin and C-peptide levels, which were reserved for periods of poor glucose control.

Over time, hypoglycemic episodes recurred, and imaging revealed disease progression. As a second-line treatment, peptide receptor radionuclide therapy was offered, but the patient declined due to the isolation requirements associated with this therapy. Consequently, everolimus was added to her octreotide regimen as a second-line agent. This combination provided excellent glucose control; however, after four months, she developed pulmonary fibrosis, a known adverse reaction to the drug.[7] She recovered after discontinuing everolimus and receiving supportive management with steroids. The patient was then switched to a combination of capecitabine and temozolomide, which she continued for four months. During this period, her functional status declined significantly, and her blood glucose levels intermittently dropped, suggesting incomplete suppression of insulin production. Due to her frailty, she was no longer a candidate for further local or systemic therapies. After a thorough discussion of her goals of care with her and her husband, she chose to transition to comfort measures. Approximately two years after her initial presentation, she passed

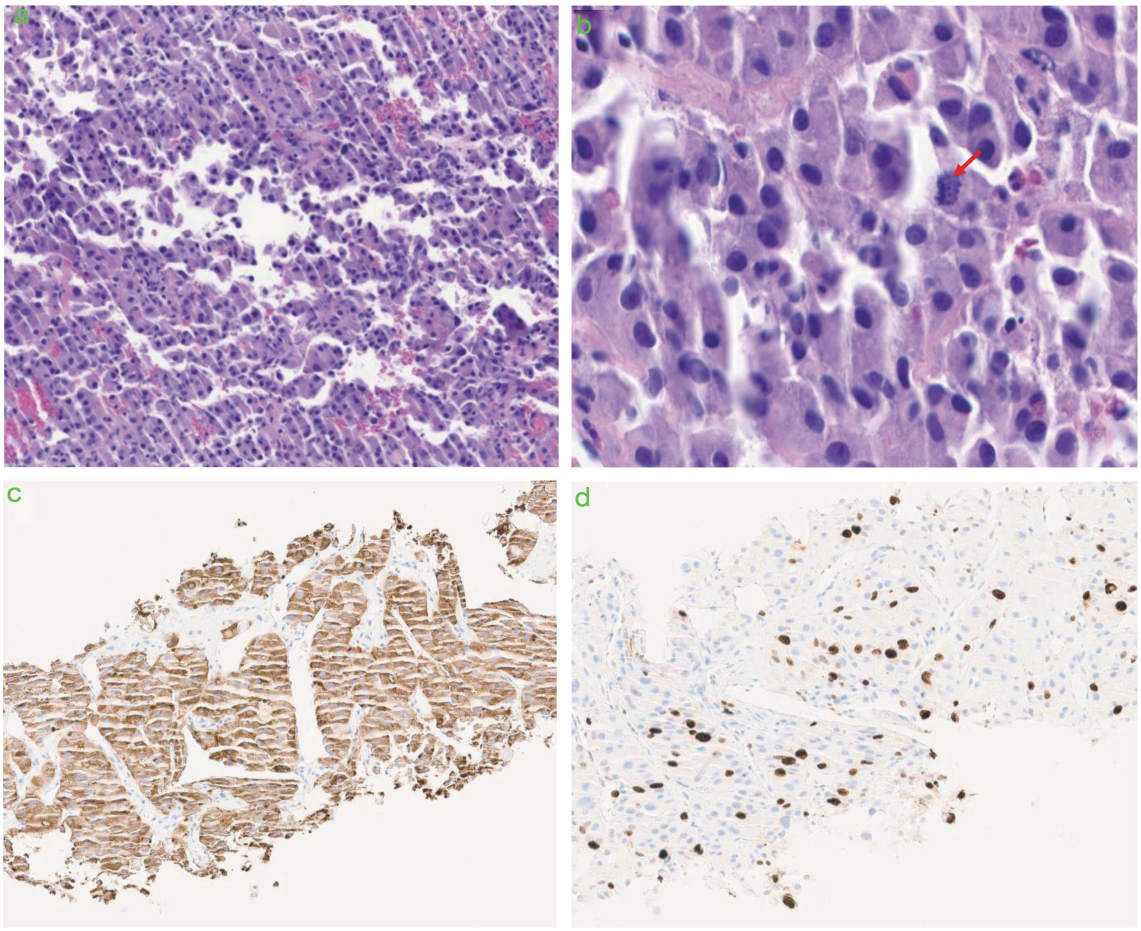

Fig. 3. Pathology from liver biopsy (a) H&E low power, (b) high power showing a mitotic figure, (c) positive synaptophysin stain, (d) Ki67. The Ki67 proliferative index was 25–30% and the mitotic count 4 mitoses in 10 high power fields. H&E, hematoxylin and eosin.

away at home on hospice (Fig. 4).

The patient is deceased, and her family declined to comment.

Discussion

Changes in diagnosis or prognosis based on second opinions are widely recognized in oncology, especially for rare malignancies such as NETs, including insulinomas, where comprehensive immunohistochemistry studies are commonly advised.[8–11] In our case, the imaging appearance suggestive of HCC and elevated AFP levels were misleading, causing the calcification in the tail of the pancreas to be overlooked, as such calcifications can sometimes be benign findings. Additionally, hypoglycemia can result from both insulinoma and HCC, necessitating further laboratory testing to differentiate between these causes.

At our institution, it is standard practice for all new patients to have their pathology and radiology reviewed to ensure diagnostic accuracy. A 2023 retrospective study from our institution found

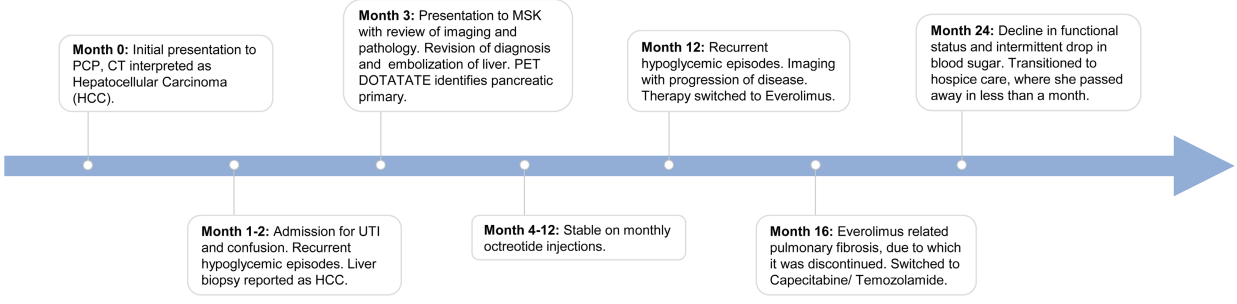

Fig. 4. Clinical timeline of disease progression and management. CT, computed tomography; MSK, Memorial Sloan Kettering Cancer Center; PCP, Primary Care Provider; PET, positron emission tomography; UTI, urinary tract infection.

Table 2. Expected laboratory parameters in patients with hypoglycemia, based on etiology

	Insulinoma	Iatrogenic	HCC	NICTH
Glucose	Very low	Low	Normal	Low
Serum insulin	Elevated	Elevated	Normal	Low
C-peptide	Elevated	Normal	Normal	Low
Proinsulin	Elevated	Normal	Normal	Low
Alpha fetoprotein	Normal	Normal	Elevated	Normal

HCC, hepatocellular carcinoma; NICTH, non-islet cell tumor hypoglycemia.

that, out of 120 cases referred for second opinions across various cancers, 42 cases had clinically significant changes in treatment, with 13 of these due to changes in diagnosis.[12] In a study by Arista-Nasr *et al*.[13] assessing the pathologic resemblance of metastatic NET of the liver to HCC, 7 cases of NET were identified out of 285 hepatic biopsies where the original diagnosis had been HCC. Similarly, in a series by Prosser *et al*.,[14] four of ten liver biopsies initially diagnosed as HCC were later reclassified as NET. This study further elaborates on the pathologic features that help differentiate atypical presentations of these diagnoses. In general, pancreatic NET (PNET) is a part of the differential diagnosis of well-differentiated HCC when presenting in the liver, because histologically both tumor types can have abundant eosinophilic cytoplasm. Therefore, a high index of suspicion for PNET is important when reviewing HCC pathology.

Insulinoma is an insulin-secreting PNET that leads to extremely low blood sugar. If left untreated, it can result in confusion, abnormal behavior, coma, and/or death.[15] While insulinomas are typically indolent, a small subset, less than 6%, with an annual incidence ranging from 0.0 to 0.27 cases per million person-years, can present as metastatic disease, most commonly involving the liver and lymph nodes.[3] The clinical presentation of insulinoma can be described using Whipple's Triad: hypoglycemic symptoms, fasting blood glucose levels below 50 mg/dL, and relief of symptoms after glucose administration.[15,16] The two key differential diagnoses to consider when insulinoma is suspected are exogenous hypoglycemia and HCC. To differentiate insulinoma from exogenous hypoglycemia, patients with insulinoma typically present with absence of plasma sulfonylurea, increased serum insulin and proinsulin levels, and elevated C-peptide levels, as summarized in Table 2.[15,17–21]

AFP is a nonspecific tumor marker, and while elevated levels are commonly associated with HCC, numerous alternative causes exist for AFP elevation, including large liver metastases from non-HCC malignancies.[22–24] AFP elevation in insulinoma is extremely rare, likely due to the rarity of insulinoma itself, though it has been reported in the literature.[25] As mentioned above, the elevated AFP levels in this case represented a significant red herring that contributed to the diagnostic challenge. To contextualize our patient's AFP findings, we identified three prior reports of AFP-positive insulinomas. Table 3 summarizes their key features, including patient demographics, AFP levels, pathology, treatments, and outcomes.[25–27] These cases, like ours, involved metastatic disease with elevated AFP and were managed with diverse interventions such as surgery, embolization, and chemotherapy. In contrast to the other cases, our patient's markedly elevated AFP level, combined with focal immunohistochemical AFP positivity, added significant diagnostic complexity and contributed to the initial misclassification as HCC.

Since clinical presentation and tumor markers such as AFP are insufficient to differentiate between these two etiologies, clinical imaging plays a crucial role in localizing insulinomas, detecting metastatic disease, and guiding management strategies.[15,28] Non-invasive imaging modalities such as CT and magnetic resonance imaging offer moderate sensitivity (33–64% and 40–90%, respectively) for lesion detection and are safe and efficient for patients.[28] However, because up to 90% of insulinomas are smaller than 2 cm, conventional imaging techniques like CT and magnetic resonance imaging can be challenging for diagnosis.[29] To address this, PET-DOTATATE, a functional scan using a radioligand targeting somatostatin receptors, can detect lesions as small as 6 mm.[29] NETs commonly overexpress somatostatin receptor subtype 2, which Ga-68 DOTATATE specifically targets, making PET-DOTATATE valuable for differentiating NETs from other etiologies.[29]

Immunohistochemistry is essential for diagnosing insulinoma and differentiating it from other tumors. Positive markers include synaptophysin, chromogranin, ISL1, INSM1, insulin (though insulin positivity is not required for diagnosis), proinsulin, amylin, and islet amyloid polypeptide.[30] Additional markers include β-catenin and PDX1 (a beta-cell marker positive in indolent types with variable staining in aggressive forms), and ARX (an alpha-cell marker negative in indolent types and positive in aggressive subtypes).[31] In contrast, tumor markers for HCC include Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3), which is more specific for HCC than total AFP, des-gamma-carboxy prothrombin, and Glypican-3, a useful diagnostic marker that distinguishes HCC from benign hepatocellular lesions.[32,33]

Once insulinoma is diagnosed and the tumor localized, surgical resection is recommended for all benign tumors, which comprise more than 90% of cases.[29] Most benign insulinomas are sporadic, and surgical excision offers potential for cure.[15] Medical management beyond surgery includes dietary modifications to prevent symptomatic hypoglycemia and medications such as diazoxide to inhibit insulin release.[15] Malignant insulinomas have a 10-year survival rate of about 29%, and treatment options include liver transplant, liver resection, chemoembolization, radiofrequency ablation, hormonal therapy with long-acting octreotide, radionuclide therapy, and/or chemotherapy for advanced disease.[28]

HCC remains a leading cause of cancer-related death in the United States, ranking ninth overall.[34] Traditionally, HCC diagnosis does not require tissue biopsy in patients with cirrhosis or high-risk chronic hepatitis B infection.[35] Additionally, patients with advanced HCC and other mesenchymal tumors can develop NICTH, a serious paraneoplastic syndrome characterized by tumor secretion of elevated IGF-2 levels, resulting in hypoglycemia, as outlined in Table 2.[1,2] NICTH is rare, and its incidence remains unknown.[4] Hypoglycemia in HCC can present in two forms: Type A and Type B. Type A is mild, typically occurring in large, rapidly growing tumors, while Type B is rare, more severe, and involves elevated levels of incompletely processed IGF-2.[2] Unfortunately,

Table 3. Summary of reported AFP-positive insulinoma cases and clinical outcomes

Reference	Patient (age/sex)	Primary tumor (location and size)	Metastatic sites	Pathology and markers	AFP levels (ng/mL)	Treatments	Outcome
Hirshberg *et al.*, 2005[25]	82 F	Liver (metastatic insulinoma; size NR)	Liver	Metastatic insulinoma	Initially, 40 and dropped to 23 after treatment	Percutaneous radiofrequency ablation	Hypoglycemia returned after four months. No further treatment due to other comorbidities
Lam *et al.*, 2001[26]	64 F	Pancreatic tail, 7 × 4 × 4 cm	Liver	Islet cell carcinoma with focal hepatoid differentiation (chromogranin+, insulin+, glucagon+, AFP+)	Increase from 1,694 to 2,119 20 months post treatment	1. Octreotide and diazoxide (ineffective). 2. Hepatic arterial embolization (failed). 3. Distal pancreatectomy, splenectomy, cholecystectomy. 4. 2× Transarterial hepatic chemoembolization. 5. 6× sequential chemotherapy. 6. Repeat transarterial hepatic chemoembolization (no response)	Tumor regressed more than 50%, and the patient was normoglycemic at 16 months. Liver metastases progressed with recurring hypoglycemia and hyperinsulinemia. Died 22 months after presentation
Shimoike *et al.*, 1997[27]	28 M	Pancreatic tail (highly vascular; size NR)	Liver	Acinar islet ("amphicrine") carcinoma (AFP+, alpha 1-antichymotrypsin+, chromogranin A+, and neuron-specific enolase+)	2,234 (increased with metastases)	NR	Progressive hepatic metastases; duration and outcome NR

AFP, alpha-fetoprotein; F, female; M, male; NR, not reported.

no standardized treatment protocol exists for hypoglycemia induced by HCC.

Primary treatment for malignancy-induced hypoglycemia focuses on controlling blood glucose, as untreated hypoglycemia can lead to severe complications.[36] Intravenous glucose administration is commonly used but typically provides only short-term relief, as it does not address the underlying tumor.[36] Secondary treatments include systemic chemotherapy and locally directed therapies such as surgical resection, liver transplantation, and trans-arterial chemoembolization (TACE), with the latter three being more common.[2] TACE targets the liver's dual blood supply system by blocking blood flow to the tumor while sparing normal tissue. Some studies have shown that TACE improves six-month survival in HCC patients and has been used to treat HCC-induced hypoglycemia.[36]

Learning points/take-home messages

Metastatic insulinoma is a rare condition that can be challenging to diagnose, particularly when the primary tumor is small and easily overlooked. Immunohistochemical markers and functional imaging, such as positron emission tomography-DOTATATE, are crucial in identifying the underlying etiology of the tumor.

The clinical presentation of hypoglycemia remains relatively uniform, irrespective of etiology. Therefore, clinicians must maintain a high index of suspicion for paraneoplastic causes of hypoglycemia.

Neuroendocrine tumors are important differentials to consider when analyzing the pathology of well-differentiated hepatocellular carcinoma, especially when presenting with isolated liver lesions.

Conclusions

Metastatic insulinoma is a rare condition that can be challenging to diagnose. Although hypoglycemia has multiple potential causes, its clinical presentation remains relatively uniform, requiring clinicians to maintain a high index of suspicion for less common etiologies such as insulinoma. The rarity of this pathology increases the risk of misdiagnosis, especially when the primary pancreatic tumor is too small to be detected on initial imaging. Therefore, a comprehensive approach incorporating multiple diagnostic modalities is essential to distinguish insulinoma from other malignancies with similar presentations and to ensure appropriate treatment selection.

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Conflict of interest

Dr. Devika Rao holds stock in Merck and Novartis. There are no other conflicts of interests.

Author contributions

Conception and design (DS, DR), literature review (JT, DS), collection and assembly of data (JT, DR), pathology imaging and interpretation (EV), radiology imaging and interpretation (SC), care of patient described (DR), and manuscript writing (DS, DR, JT,

EV, SC). All authors have approved the final version and publication of the manuscript.

Ethical statement

The study was performed in accordance with the ethical standards of the institutions with which we are affiliated and with the Declaration of Helsinki (as revised in 2024). Written informed consent was obtained from the patient for publication of this case report. All imaging and pathology materials were fully de-identified in accordance with journal guidelines and ethical standards.

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