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Case Report

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Paraneoplastic Hypoglycemia Secondary to Clear Cell Renal Cell Carcinoma: An Unusual Case with Acute Neurological Presentation

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ABSTRACT

Introduction: Non-insulin-mediated hypoglycemia in non-diabetic patients is an uncommon clinical finding and may be associated with extrapancreatic neoplasms, such as IGF-2–secreting tumors. We report a case of severe hypoglycemia in a patient with clear cell Renal Cell Carcinoma (ccRCC).

Case Presentation: A 71-year-old male was admitted after an episode of syncope accompanied by seizures and confusion. Capillary blood glucose was measured at 10 mg/dL, requiring continuous dextrose infusion. Laboratory workup excluded insulinoma and showed elevated C-peptide levels. Abdominal CT revealed a right renal mass, and radical nephrectomy confirmed a pT1b clear cell renal cell carcinoma. Hypoglycemia resolved completely following tumor resection.

Discussion: Non–Islet Cell Tumor Hypoglycemia (NICTH) due to IGF-2 overproduction ("big IGF-2") is a rare paraneoplastic syndrome typically associated with solid tumors, including renal carcinomas. Diagnosis requires exclusion of alternative causes and demonstration of clinical resolution after tumor removal.

Conclusion: Paraneoplastic hypoglycemia should be suspected in patients with visceral tumors and unexplained hypoglycemia in the absence of hyperinsulinemia. Early recognition may allow for curative surgical treatment.

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Introduction

Spontaneous hypoglycemia in non-diabetic individuals is rare and may result from pharmacologic, endocrine, infectious, or neoplastic causes. One uncommon etiology is Non–Islet Cell Tumor Hypoglycemia (NICTH), a paraneoplastic syndrome usually associated with mesenchymal or epithelial tumors that secrete an incompletely processed, high-molecular-weight form of insulin-like growth factor 2 (IGF-2), commonly referred to as "big IGF-2," which exerts insulin-like effects [1].

Clear cell Renal Cell Carcinoma (ccRCC) is only rarely associated with hypoglycemia, though sporadic cases have been reported in the literature. [2,3] We present a case of severe hypoglycemia with seizures as the initial manifestation of renal carcinoma, initially suspected to represent Doege–Potter syndrome.

Case Report

A 71-year-old male with a history of hypertension controlled with losartan, and no prior diagnosis of diabetes or other significant comorbidities, presented to the emergency department following a sudden episode of collapse preceded by generalized tremors, confusion, and progressive loss of consciousness. Upon arrival, he experienced a generalized tonic-clonic seizure lasting approximately two minutes, without sphincter release or a postictal state.

Vital signs on admission were: blood pressure 130/70 mmHg, heart rate 70 bpm, respiratory rate 21 rpm, oxygen saturation 98%, and temperature 36 °C. Capillary blood glucose was found to be 10 mg/dL. An intravenous bolus of dextrose was administered, followed by continuous infusion of 5% dextrose. The patient required a constant glucose infusion to maintain blood glucose levels between 100 and 140 mg/dL.

Initial laboratory tests showed normal serum cortisol levels (3.9 mcg/dL) and elevated C-peptide levels (2.99 ng/mL; reference range: 0.7–1.9 ng/mL). No electrolyte, hepatic, or renal abnormalities were detected.

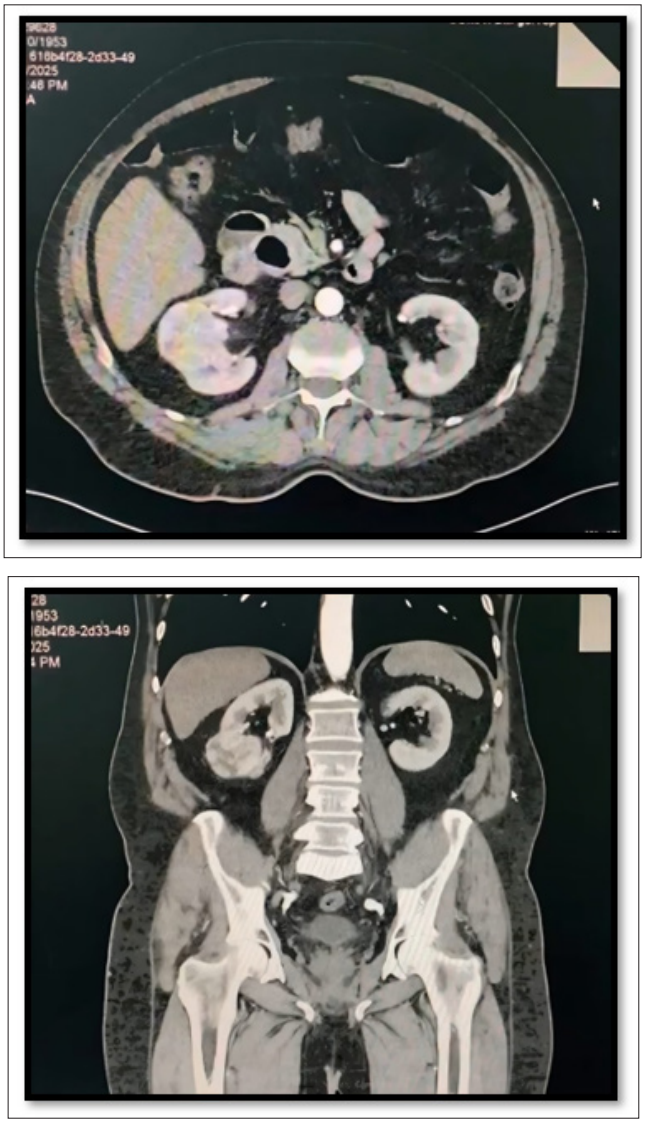

Figure 1: Expansive tumor mass formation located in the mid-to-lower third of the right renal parenchyma, causing bulging of the capsular contour and medial extension into the renal sinus. It exhibits a centrally located, irregular, contrast-enhancing area suggestive of possible necrosis. The lesion measures approximately 6.5 × 5 × 4.8 cm in the transverse, anteroposterior, and craniocaudal axes, respectively.

Given the persistent hypoglycemia in the absence of apparent hyperinsulinemia, a contrast-enhanced abdominal and pelvic Computed Tomography (CT) scan was performed. It revealed an expansive, solid-appearing mass in the right kidney, suspicious for neoplastic proliferation (Figure 1). Based on these findings, exploratory laparotomy was indicated. Intraoperatively, a solid tumor measuring 5×5×4 cm was identified in the mid-to-lower pole of the right kidney. A radical right nephrectomy was performed (Figure 2).

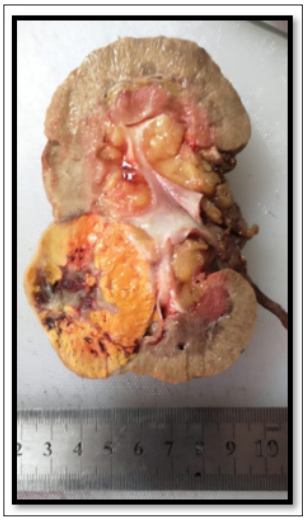

Figure 2: The right kidney measures 10.5 × 6.3 × 4 cm. The external surface is irregular due to a lobulated protrusion at the lower pole, measuring 5 cm. On sectioning, a well-defined, solid, tumor-like lesion is observed, measuring 5 × 5 × 4 cm, with a yellowish coloration

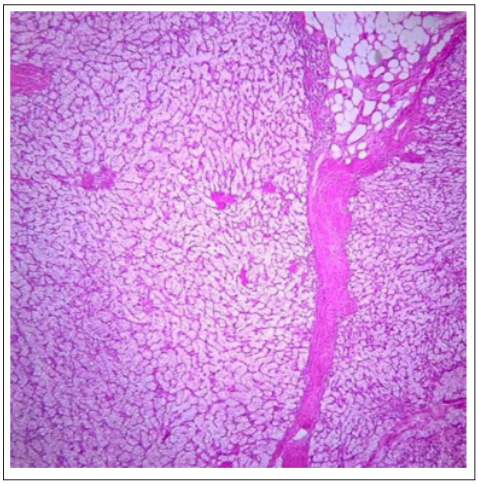

Figure 3A: 40× magnification: Clear cell renal cell carcinoma is observed, with expansive borders extending focally into the renal sinus fat

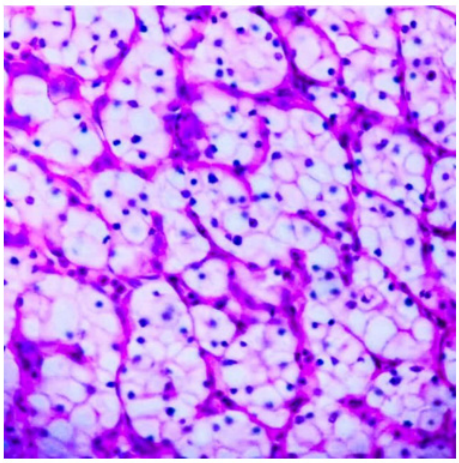

Figure 3B: 400× magnification: The tumor is composed of cells with clear cytoplasm due to the presence of glycogen and lipids, displaying a solid growth pattern. The nuclei are of moderate size, with no rhabdoid or sarcomatoid features. ISUP/WHO grade 2.

Histopathological analysis confirmed the diagnosis of clear cell renal cell carcinoma (Figure 3A/B), staged as pT1b, pNx, pMx. On the first postoperative day, the patient exhibited normoglycemia (100–120 mg/dL) without the need for glucose supplementation. Blood glucose levels remained stable throughout the hospital stay, and the patient was discharged in good condition.

Discussion

Hypoglycemia in non-diabetic patients is an uncommon clinical presentation, and in the setting of a solid tumor, it should raise suspicion for a paraneoplastic syndrome. In this case, the patient experienced a seizure secondary to severe hypoglycemia (capillary glucose 10 mg/dL) with no history of insulin therapy or hypoglycemic agents, pointing toward a non-pancreatic etiology.

The underlying pathophysiological mechanism is known as **Non-Islet Cell Tumor Hypoglycemia (NICTH)**, a paraneoplastic syndrome associated with the secretion of an incompletely processed, high-molecular-weight form of insulin-like growth factor 2 (IGF-2), referred to as "big IGF-2." This molecule exerts insulin-like effects by:

- Activating insulin and IGF-1 receptors,
- Enhancing peripheral glucose uptake in insulin-sensitive tissues,
- Suppressing hepatic glucose production (both gluconeogenesis and glycogenolysis),
- Inhibiting endogenous insulin secretion and the counterregulatory hormonal axis (growth hormone and ACTH).

This leads to a clinical picture of hypoglycemia with low insulin, C-peptide, and β-hydroxybutyrate levels. In our patient, C-peptide was slightly elevated (2.99 ng/mL), which may represent a transient physiological response to glucose infusion or a laboratory artifact. The absence of exogenous insulin use, along with normal cortisol levels and rapid resolution of hypoglycemia following tumor resection, strongly supports a paraneoplastic mechanism.

Historically, Doege-Potter syndrome-hypoglycemia caused by a solitary fibrous tumor (SFT), most commonly of pleural origin-was one of the first described causes of NICTH. Due to the severe hypoglycemia in the absence of insulinoma and initial imaging suggesting a mesenchymal mass, this diagnosis was initially considered. However, histopathological examination confirmed clear cell Renal Cell Carcinoma (ccRCC), ruling out SFT and broadening the spectrum of epithelial tumors capable of inducing paraneoplastic hypoglycemia.

Clear cell RCC is the most common histological subtype of renal cancer (accounting for 75–85%) and is known to be associated with various paraneoplastic syndromes, including polycythemia, hypercalcemia, hypertension, and rarely, hypoglycemia [1,2]. This tumor arises from the proximal renal tubular epithelium, is often highly vascularized, and may secrete multiple bioactive peptides ectopically.

Fewer than 50 cases of hypoglycemia associated with ccRCC have been documented in the medical literature. Complete resolution of hypoglycemia after surgical removal of the tumor provides strong support for a functional diagnosis of NICTH [3,4]. In this case, radical right nephrectomy led to immediate normalization of blood glucose levels, an indirect but highly suggestive marker of removal of the paraneoplastic stimulus. From a surgical perspective, management of renal masses should be individualized based on tumor stage, size, and patient comorbidities. This patient had a T1b ccRCC (tumor >4 cm but ≤7 cm, confined to the kidney), for which curative treatment through radical nephrectomy or partial nephrectomy (in selected cases) is indicated [5,6].

This case underscores the importance of comprehensive evaluation in patients with unexplained hypoglycemia. In the presence of a solid mass, surgical intervention should be considered not only for oncological control but also as a potentially curative treatment for the associated metabolic syndrome. Furthermore, it highlights the value of a **multidisciplinary approach** in the management of tumors presenting with atypical clinical features. Collaboration among internal medicine, endocrinology, surgery, and pathology was essential to establish the definitive diagnosis and ensure successful clinical resolution.

Conclusion

This case illustrates the importance of considering paraneoplastic etiologies in non-diabetic patients presenting with severe hypoglycemia. The identification of a renal mass, together with the rapid postoperative normalization of blood glucose, strongly supports the diagnosis of IGF-2–mediated tumor-induced hypoglycemia. Radical nephrectomy was curative. Early recognition of this syndrome can lead to prompt diagnosis and potentially definitive treatment.

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