Insulinoma and Chronic Kidney Disease: An Uncommon Conundrum Not to Be Overlooked

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ABSTRACT: A hypertensive man with chronic kidney disease (CKD) secondary to polycystic disease was hospitalized for symptoms related to hypoglycemia. Fasting test elicited symptomatic hypoglycemia after 12 hours, which was associated with inappropriately unsuppressed normal insulin and C-peptide levels. Neither ultrasonography (US) nor magnetic resonance imaging detected any pancreatic tumor. Endoscopic ultrasonography (EUS) showed a small isoechogenic nodule suspect for neuroendocrine tumor in the pancreatic head. 68Gallium-DOTA-Tyr3-octreotide positron emission tomography/computed tomography revealed intense uptake by a small region in the pancreatic head. Surgical exploration together with intraoperative US confirmed the nodule in the pancreatic head and evidenced another hypoechoic one in the uncinate process. Both nodules were enucleated, but only the latter, which had not been previously detected by EUS, proved compatible with insulinoma on combined histology and immunohistochemistry. After nodule enucleation, hypoglycemia resolved and did not relapse. Insulinoma, as a major cause of unexplained hypoglycemia, requires careful hormonal and instrumental workup. In patients with CKD, the interpretation of biochemical criteria for the diagnosis of insulinoma can be challenging. Localization techniques may display pitfalls. Surgery is curative in most patients but long-term follow-up is required.

KEYWORDS: Hypoglycemia, insulinoma, fasting test, chronic kidney disease, 68Gallium-DOTATOC PET/CT, surgery

Introduction
Insulinoma is the most common (25%-40%) functioning pancreatic neuroendocrine tumor. This tumor is mostly benign, small (<2 cm), and equally distributed throughout the pancreas; its incidence is low ranging from 1 to 4 cases per million persons per year.1,2 Apart from factitial hypoglycemia, insulinoma is the most common cause of hypoglycemia in otherwise healthy patients. This tumor is characterized by erratic hyperinsulinemia leading to symptomatic hypoglycemia, which is manifested by the classic Whipple triad: hypoglycemia, autonomic, and neuroglycopenic symptoms and prompt reversal of such symptoms after the administration of glucose.1–3 The diagnosis of insulinoma is often delayed because of its multifaceted symptoms, which may be misattributed to cardiac, neurological, or psychiatric disorders. The 72-hour fasting test is used to document Whipple triad and ascertain the cause (insulin-mediated vs noninsulin-mediated) of the hypoglycemia.1,3,4 In patients with chronic kidney disease (CKD), the interpretation of β-cell polypeptide levels can be challenging because they are often increased as a result of the reduced clearance.5

Insulinoma can be detected by contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) or by endoscopic ultrasonography (EUS) (1, 2). In addition, because up to 50% of these tumors express somatostatin receptors (mostly type2, sst-2), functional imaging, such as octreoscan (111Indium-pentetreotide) and, more recently, 68Gallium somatostatin receptor positron emission tomography (PET) may be used in the diagnostic workup.2,4,5

We report the case of a hypertensive man with CKD due to polycystic disease who had been hospitalized for symptomatic hypoglycemia. Insulinoma was eventually diagnosed by means of combined fasting test, functional imaging, intraoperative ultrasonography (IOUS), and histology/immunohistochemistry of a surgically resected pancreatic tumor of the uncinate process, after preoperative EUS had failed to properly localize the tumor. After surgery, the patient’s symptoms and hypoglycemia resolved and did not relapse.

Case Report
A nondiabetic 59-year-old man having sudden mental confusion, speech difficulty, and uncoordinated movements was evaluated at home by the territorial emergency team. The patient looked pale and sweaty, blood pressure was normal, and hypoglycemia: 31 mg/dL was ascertained by means of hemoglotest; glucose administration by mouth normalized glycemia: 106 mg/dL and the symptoms resolved. The patient was taken to the emergency department, where he proved to be alert and asymptomatic. Hemoglucotest showed slight hyperglycemia: 127 mg/dL confirmed by blood tests (166 mg/dL); these latter also showed increased creatinine levels: 2.7 mg/dL (n.v. 0.1-1.2, glomerular filtration rate: 25 mL/min). No metabolic acidosis...
was found on hemogasanalysis. An electrocardiogram revealed sinus rhythm with signs of left ventricular hypertrophy, whereas chest X-ray was normal. The patient was hospitalized in our Internal Medicine ward.

Anamnesis was remarkable for hypertension on therapy with irbesartan plus hydrochlorothiazide and polycystic kidney disease with secondary stage-3 CKD; the patient was also on calcitriol for secondary hyperparathyroidism and denied taking any drug that might cause hypoglycemia. His wife reported that in the early morning or late evening over the previous few months, her husband had experienced a few episodes of mental confusion. In particular, the patient had had a minor car accident 3 months earlier due to sudden loss of consciousness; subsequent brain CT and MRI, electroencephalography, and Holter electrocardiogram proved unremarkable.

A fasting test was conducted and, after 12 hours, showed the occurrence of symptomatic hypoglycemia associated with unsuppressed "normal" insulin and C-peptide levels (Table 1). The test was discontinued and 5% glucose infusion was administered, with reversal of symptoms. On suspicion of insulinoma, abdominal US was performed, which showed the known polycystic kidney and liver disease; however, no pancreatic mass was found, even on subsequent MRI (performed without contrast media, owing to CKD) which better characterized the hepatorenal polycystic disease (Figure 1). By contrast, EUS revealed a 1-cm isoechogenic nodule in the superior part of the pancreatic head and adjacent to the gastro-duodenal artery, which was deemed suspect for neuroendocrine tumor (NET) (Figure 2A). Fine-needle aspiration (FNA) of the suspect nodule was deemed too risky. 68Gallium DOTA-Tyr3-octreotide (DOTATOC) PET/CT showed an intense uptake (SUV max: 16) by a small region of the pancreatic head (Figure 3). Multiple endocrine neoplasia type 1 (MEN-1) was excluded, given the normality of pituitary-gonadal, pituitary-adrenal, and pituitary-thyroid axes and calcium levels (Table 2).

Table 1. Fasting test results in the patient studied.

| TIME       | GLUCOSE LEVELS, mg/dl | INSULIN LEVELS*, μU/ml | C-PEPTIDE LEVELS*, ng/ml |
|------------|-----------------------|------------------------|-------------------------|
| 8 AM       | 68                    | 4.0                    | 2.0                     |
| 12 PM      | 65                    | 5.0                    | 2.2                     |
| 4 PM       | 54                    | 3.8                    | 1.6                     |
| 6 PM       | 48                    | 5.6                    | 1.8                     |
| 7 PM       | 40                    | 5.1                    | 1.7                     |
| 8 PM (symptomatic) | 37 | 4.1 | 1.7 |

*aImmunochemiluminescence assay, sensitivity: 0.2 μU/ml.
*bImmunochemiluminescence assay, sensitivity: 0.05 ng/ml.

Figure 1. Magnetic resonance imaging without contrast, showing an advanced picture of hepatorenal polycystic disease.

After multidisciplinary discussion, surgery was scheduled. In the meantime, therapy with diazoxide was proposed, but the patient declined. During surgery, continuous 5% glucose and somatostatin (to reduce insulin secretion) infusion was performed, and the nodule observed during EUS in the superior part of the pancreatic head was found, as was another nodule in the uncinate process (1.5 cm maximum diameter); this latter was hypoechoic on IOUS (Figure 2B). Both nodules were enucleated, and a drainage was left in place. Only the nodule in the uncinate process was diagnosed as an NET on intraoperative frozen section histology.

The patient was transferred to the intensive care unit; hyperglycemia (245 mg/dL) occurred 7 hours after the end of surgery and insulin was administered; thereafter, glucose levels remained normal without therapy. Low-output pancreatic fistula occurred; subcutaneous octreotide (300 μg/d) and total parenteral nutrition were therefore started. Final histology showed normal pancreatic tissue in the nodule from the pancreatic head, whereas the nodule in the uncinate process proved to be an insulinoma on combined histologic and immunohistochemical evaluation (Figure 4A to C).

Over several days, the output of the fistula diminished markedly, oral nutrition was gradually restarted and, 10 days after surgery, the patient was discharged with the drainage still in place. On subsequent outpatient visits, fistula output was seen to be minimal and, 3 weeks after surgery, the drainage was removed. To date, 18 months after surgery, the patient is asymptomatic and fasting glucose levels are normal. Long-term follow-up has been scheduled.
Discussion

We report the case of a middle-aged man with long-standing CKD and recent symptomatic hypoglycemia, which had been overlooked. An insulinoma in the uncinate process of the pancreas was diagnosed by combining fasting test, 68Gallium-DOTATOC PET/CT, IOUS, and histology/immunohistochemistry, after EUS had detected a benign unspecific pancreatic nodule but not the NET.

In nondiabetic seemingly healthy persons, hypoglycemia is usually associated with exogenous hyperinsulinism due to accidental, surreptitious, or even malicious administration of insulin or an oral hypoglycemic drug; less commonly it is due to endogenous hyperinsulinism secondary to β-cell tumors, insulin autoimmune disorders, or nesidioblastosis.3,4

In both endogenous and exogenous hyperinsulinism, hypoglycemia is associated with unsuppressed insulin levels. However, whereas endogenous hyperinsulinism shows a simultaneous rise in C-peptide and proinsulin levels, these latter are undetectable in exogenous hyperinsulinism.3,4

Chronic kidney disease is an independent risk factor for hypoglycemia; indeed, the kidney is the main site of insulin clearance by receptor-mediated degradation by the tubular epithelial cells and removes approximately 50% of peripheral insulin and 70% of C-peptide by glomerular filtration.

Hence, β-cell polypeptide levels are often increased in patients with CKD, but this does not usually cause spontaneous hypoglycemia unless other causes are superimposed.5,8,9 In patients with CKD, spontaneous hypoglycemia is uncommon: 3.6% in 2 large case series,10,11 the first of which included only 2.5% of diabetic patients.10

Indeed, in patients with CKD, spontaneous hypoglycemia can be associated either with inappropriately increased insulin levels or decreased/undetectable insulin levels.5 The latter conditions include malnutrition, infections, alcohol abuse, multiorgan failure, drugs, and adrenal insufficiency. In CKD, the presence of diabetes significantly increases the rate of hypoglycemia, which is usually due to insulin or hypoglycemic drug administration.11

Our patient had stage-3 CKD and denied taking any drug that might induce hypoglycemia; he was normo-nourished, no
alcohol abuse or infection were present, and adrenal insufficiency was ruled out by normal cortisol levels.

To our knowledge, only 3 cases of insulinoma in patients with end-stage CKD have been reported; the first patient, who had previously undergone renal transplantation without resuming normal renal function, had increased insulin levels: 52 μU/mL during symptomatic hypoglycemia and underwent successful surgery; the second was on peritoneal dialysis, and near-continuous provision of glucose in the peritoneal dialysis fluid concealed hypoglycemia symptoms of an insulinoma, which were revealed when peritoneal dialysis was temporarily interrupted. Finally, the third patient, who had type 2 diabetes and was on hemodialysis, showed increased insulin levels: 22.9 μU/mL associated with low-normal glycemic levels; he refused surgery and was successfully treated with diazoxide.

The fasting test, together with Whipple triad, is a key tool for the diagnosis of insulinoma, which typically features glucose levels <55 mg/dL (3 mmol/L), insulin levels ≥3 μU/mL (18 pmol/L), and C-peptide levels ≥ 0.6 ng/mL; although rarely assayed in clinical practice, proinsulin is >5 pmol/L and β-hydroxybutyrate <2.7 mmol/L.

Because β-cell polypeptides levels are often increased in patients with CKD, their interpretation in this setting remains challenging, and confirmation of a suspected insulinoma depends on identification by localization procedures.

In our patient, the results of the fasting test aroused suspicion of insulinoma, as hypoglycemia occurred after 12 hours and was associated with inappropriately unsuppressed, “normal” insulin and C-peptide levels, despite the presence of CKD.

Our findings hold an important message for clinicians, as “normal” insulin levels during hypoglycemia do not exclude the diagnosis of insulinoma, even in patients with CKD.

Plasma insulin levels are now measured by means of specific assays (immunoochemiluminescence or immunoradiometric

Table 2. Main laboratory tests in the patient studied.

| Test | Value | Reference Range |
|------|-------|-----------------|
| Creatinine, mg/dL (n.v. 0.6-1.2) | 2.7 | |
| LH, IU/L (n.v. 1.7-8.6) | 7.3 | |
| FSH, IU/L (n.v. 1.5-12.4) | 4.3 | |
| Testosterone, ng/ml (n.v. 3-8) | 3.5 | |
| FT4, ng/dl (n.v. 0.9-1.7) | 1.3 | |
| TSH, μIU/ml (n.v. 0.27-4.2) | 4 | |
| Cortisol, μg/dl (n.v. 6.2-19.4, 7-10 am) | 18.9 | |
| PTH, pg/ml (n.v. 15-65) | 166 | |
| Calcium, mg/dl (n.v. 8.2-10.2) | 8.5 | |

Abbreviations: LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; PTH, parathyroid hormone.

Figure 4. (A) The nodule removed from the uncinate process of the pancreas featured trabecular-insular architecture with cubic/polygonal cells, sparsely granulated cytoplasm, and round and slightly dysmorphic nuclei (hematoxylin-eosin, ×20). (B) Immunohistochemistry showed faint homogeneous cytoplasmatic positivity for insulin (3,3′-diaminobenzidine staining, ×20). (C) Ki-67% labeling index of the tumor cells was low: 1% (arrow, ×20). A final diagnosis of well-differentiated (G1) insulinoma was made.
In both the fasting and postprandial states in 21%, and exclu-
sing that hypoglycemia occurred solely in the fasting state in 73%,
hypoglycemia was ascertained. Occurred mostly during fasting, as during hospitalization when 
72 hours in as-yet asymptomatic patients, to minimize failure 
however, this author recommended prolonging fasting up to 
hypoglycemia within 48 hours of the beginning of fasting; 
most (93%) of 170 patients with insulinoma had symptomatic 
uptake of the tracer by a small region of the pancreatic head, 
where the insulinoma was located intraoperatively and removed.

In our patient, symptoms subsequently related to hypogly-
cemia had started a few months before hospitalization and 
occurred mostly during fasting, as during hospitalization when 
hypoglycemia was ascertained. Indeed, a review on 237 patients with insulinoma showed 
that hypoglycemia occurred solely in the fasting state in 73%, 
in both the fasting and postprandial states in 21%, and exclu-
sively postprandially in 6%.20

Insulinomas can be difficult to locate because 90% are 
smaller than 2 cm.1,12 In our patient, US and MRI did not detect 
any pancreatic tumor, but the sensitivity of the latter technique 
was impaired by the fact that CKD prevented the use of con-
trast medium. The sensitivity of US decreases when the tumor 
is located in the tail or head of the pancreas, and its overall 
value is low, approaching 40%.1,2 Detection rates of CT and 
MRI range widely (16%-73%).2,21 However, the sensitivity of 
dynamic CT reaches 90%.2

In our patient, EUS was performed by an expert gastroen-
derologist and detected a small nodule suspect for NET in the 
superior part of the pancreatic head. Fine-needle aspiration of 
the nodule was deemed too risky, owing to its contiguity with 
the gastro-duodenal artery. However, during surgical exploration, in addition to the sus-
p ect nodule detected on EUS (eventually proved to be normal 
pancreatic tissue on histology), IOUS detected another nodule 
in the uncinate process of the pancreas, which proved to be an 
insulinoma. Intraoperative ultrasonography can locate these 
tumors in 60% to 95% of cases.1,2 In our patient, EUS, which is 
an operator-dependent technique, failed to detect the real tumor 
located in the pancreatic uncinate process. Endoscopic ultra-
sonography pitfalls include very small and/or multiple lesions 
and pedunculated lesions arising from the pancreatic tail.22

Endoscopic ultrasonography combined with FNA is able to 
detect 40% to 94% of insulinomas, with the best detection rate 
for tumors localized in the head of the pancreas (~90%) and the 
worst for those in the tail (~40%).1,2 Combining conventional 
imaging (CT/MRI) with EUS yields a detection rate approach-
ing 100%.2,14

Up to 10% of insulinomas are associated with MEN-1 syn-
drome; these are more often malignant and multifocal.2,22 
Multifocality could not be excluded a priori in our patient but 
was unlikely because the array of hormonal data was not typical 
of MEN-1 syndrome.

The PET/CT imaging with 68Ga-DOTATOC, a tracer 
with high affinity for sst-2, possesses higher diagnostic ac-
ccuracy than octreoscan,4,23,24 Although up to 50% of insulinomas 
do not express sst-2 receptors, this was not the case of our 
patient, in whom 68Ga-DOTATOC PET/CT showed intense 
uptake of the tracer by a small region of the pancreatic head, 
where the insulinoma was located intraoperatively and removed.

In our patient, the diagnosis of insulinoma emerged from 
the combination of clinical, imaging and histologic/immono-
histochemical evaluations. However, immunostaining for insu-
lin in the pancreatic tumoral nodule proved faint. In this regard, 
immunohistochemical determination of insulin expression by 
tumor cells is not absolutely necessary for diagnosis because 
several insulinomas do not stain positively despite correct diag-
nosis, as a result of the rapid release of insulin from the tumor 
cells.25

In sum, insulinoma is an uncommon cause of unexplained 
hypoglycemia in patients with renal impairment, too.

Greater awareness among clinicians would allow proper 
biochemical and instrumental investigation and location, to 
undertake safe surgery, which is able to cure most of the patients.

Author Contributions

LF contributed to the conception, investigation, analysis of 
data, and writing of the manuscript; SP, MCS, and GA con-
tributed to the conception, design, and investigation. MF and 
SC performed surgery. AP performed endoscopic ultrasonog-
raphy. SS contributed to the analysis of the data and performed 
histology and immunohistochemistry evaluation.

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