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Insulinoma and Isolated Polycystic Liver Disease: Case Report

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Authors' contributions

This work was carried out in collaboration between all authors. Authors CMB and PAV wrote the draft of the manuscript. Author CMB managed the literature searches. Author LMBL designed the figures, TCX, ICB, CAAS and FJGP contributed to the correction of the draft. Author CMB provided the case. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Gastroenteropancreatic neuroendocrine tumors are fairly rare neoplasms and their diagnosis can result defying. Polycystic liver disease is also a rare condition characterized by the formation of liver cysts. We report a case of a 59-year-old female with isolated polycystic liver disease and hypoglycemia. The prolonged diagnostic fast indicated the presence of endogenous hyperinsulinism and after distal pancreatectomy the final histological result confirmed the presence of an insulinoma. The coexistence of these two unusual clinical conditions was unexpected and there are few reported cases associating both conditions.

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ABBREVIATIONS

PLD: Polycystic liver disease; PCLD: Isolated polycystic liver disease; ADPKD: Autosomal dominant polycystic kidney disease; NET: Neuroendocrine tumor; CT: Computed tomography; mTOR: Mammalian target of rapamycin; HbA1c: Glycated hemoglobin.

1. INTRODUCTION

Polycystic liver disease (PLD) is a rare (prevalence 1:158000) and debilitating condition characterized by the formation of more than 20 fluid-filled cysts in the liver. PLD belongs to the spectrum of fibrocystic liver diseases. Two inherited disorders associated with PLD are distinguished: isolated polycystic liver disease (PCLD) and autosomal dominant polycystic kidney disease (ADPKD). In PCLD, the polycystic liver is the major presentation. [1] Mutations in two genes, *PRKCSH* and *SEC63*, explain 20% of PCLD cases. The proteins encoded by these genes – glucosidase 2 subunit β (also known as hepatocystin) and translocation protein SEC63 homologue – are involved in the folding and the quality control of glycoproteins in the endoplasmic reticulum. Ductal plate malformation determines the resulting clinical phenotype.

Risk factors for the development of PLD are female sex, exogenous estrogens, and multiple pregnancies [1,2]. The course of PLD is progressive and can lead to severe hepatomegaly. The prevalence of liver cysts increases with age. The majority of symptomatic patients are women aged 50 years. Most common symptoms are abdominal pain and distension, dyspepsia, early satiety, feeling of fullness, dyspnea, and back pain. Complications such as cyst infection or bleeding are uncommon [1]. Treatment of PLD is only indicated in symptomatic patients and aims to reduce the volume of the polycystic liver to improve mechanical complaints. Liver transplantation is the ultimate therapy [1].

On the other hand, tumors derived from the diffuse neuroendocrine gastrointestinal system and from the pancreas are also fairly rare. Their incidence is about 2.5 to 5 cases per 100000. Insulinomas are typically small, benign, functioning tumors that clinically present with hypoglycemia. Serum markers for insulinoma include insulin, proinsulin and C-peptide. In addition, tissue expression of the proliferation marker Ki-67 helps to determine tumor grade and prognosis. Endoscopic ultrasonography can detect nearly all lesions. In most of the cases treatment is tumor enucleation and pancreatic resection when needed. Around 85-95% of pancreatic benign insulinoma cases are cured and the 5-year survival is 97% [3].

The aim of this report is to present a case with two unusual coexisting conditions: isolated polycystic liver disease and insulinoma.

2. PRESENTATION OF CASE

A 59-year-old Mexican woman was admitted to the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran in Mexico City. Her present illness started two-and-a-half years before when she noted early satiety and an enlarged abdominal circumference. After performing a complete diagnostic work-up PCLD was diagnosed. She was referred to the Endocrinology Clinic for evaluation of repeated episodes of hypoglycemia. Along with her liver disease, she had episodes of waking up feeling disorientated and with blurred vision. These events became more frequent, occurring almost daily. Frequently she woke up with behavioral changes such as aggressiveness. She reported a partial complex seizure in one occasion. To ameliorate the symptoms, she consumed frequent small meals and fruit juice. At the beginning, the symptoms were predominantly at fasting conditions, and later they also became evident in the postprandial period.

Her family history was relevant for stroke and hypertension in her mother, and diabetes in one sister. She has no significant past medical history.

During her first Endocrine consultation she reported dizziness and her capillary blood glucose was 48 mg/dl. We requested an oral glucose tolerance test with 75 grams. The results of this test are shown in Table 1.

Table 1. Oral glucose tolerance test with 75 g of glucose

	Glucose mg/dl	Insulin µU/ml
Basal	59	6.14
30 min	158	33.03
60 min	159	95.63
90 min	148	67.82
2 h	149	59.08
3 h	72	13.01
4 h	45	7.95
5 h	57	4.28

Reference values for insulin are 1.9-23 µUI/ml

Thyroid disease, adrenal insufficiency, and hepatic dysfunction were ruled out. The patient was hospitalized to perform a supervised prolonged diagnostic fast. The laboratory results during the fast are displayed in Table 2.

The fasting test was terminated after 35 and half hours, when the patient referred dizziness and tremor associated with a serum blood sugar concentration of 26 mg/dl. Determination of sulfonylureas was negative at the end of the test (Table 3).

An endoscopic ultrasonography showed a pancreatic solid hypoechoic lesion, measuring 2 x 1 cm, with irregular borders, and a heterogeneous content. A guided fine-needle aspiration biopsy was taken and reported a well-differentiated neuroendocrine tumor (NET). A triphasic abdominal computed tomography (CT) revealed a lesion localized at the tail of the pancreas (Fig. 1A). A laparoscopic distal pancreatectomy and drainage of the largest liver cyst (measuring 19 cm) were performed. Capillary glucose after surgery was 220 mg/dl. At the histopathology examination two pancreatic lesions at the tail of the pancreas were identified. A solid lesion measuring 0.9 x 0.7 cm, and a cystic lesion localized in the medial part measuring 1.1 x 1.1 cm. The diagnosis confirmed a well-differentiated NET, classic carcinoid grade 1, with negative borders, and negative perisplenic lymph nodes (0/7). Immunohistochemistry was positive for chromogranin, synaptophysin, and insulin. Ki-67 expression was <1% (Fig. 2). In the following days, capillary glucose determinations were within normal values; however, glycated hemoglobin (HbA1c) and an oral glucose tolerance test at follow up showed risk for future diabetes development (HbA1c 6.4% and 2-hour glucose 165 mg/dl). In addition, a cerebral magnetic resonance angiography showed two sacular aneurisms of 1.5 and 2 mm on the left internal carotid artery. Evaluation for liver transplant is ongoing.

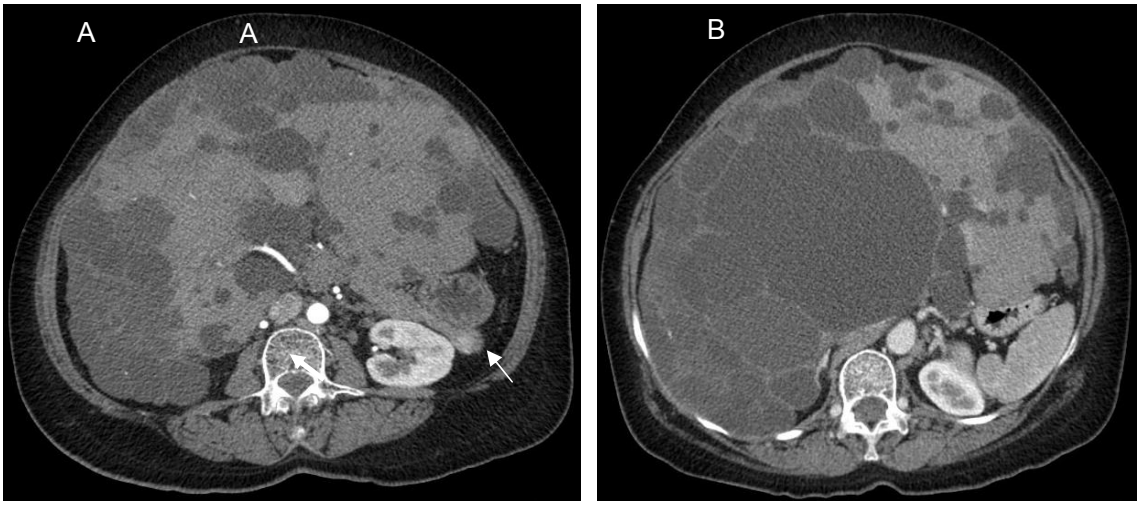

Fig. 1. CT scan of the pancreas. A. Arterial phase showing a lesion with contrast reinforcement (arrow). B.Venous phase showing polycystic liver disease

Table 2. Biochemical variables during the diagnostic fast

Day	Time	Glucose mg/dl	Insulin µU/ml	C-peptide ng/ml	Proinsulin pmol/l
1	17:58	84	12.83		
2	24:04	67	6.73		
	5:48	59	6.65		
	11:54	42	11.28		
	18:06	32	4.52	3.13	68.9
	23:58	35	4.84		
3	5:24	26	9.40	2.46	75.3

Reference values for insulin, C-peptide, and proinsulin are 1.9-23 µUl/ml, 0.8-3.1 ng/ml, and 0-18.8 pmol/l, respectively

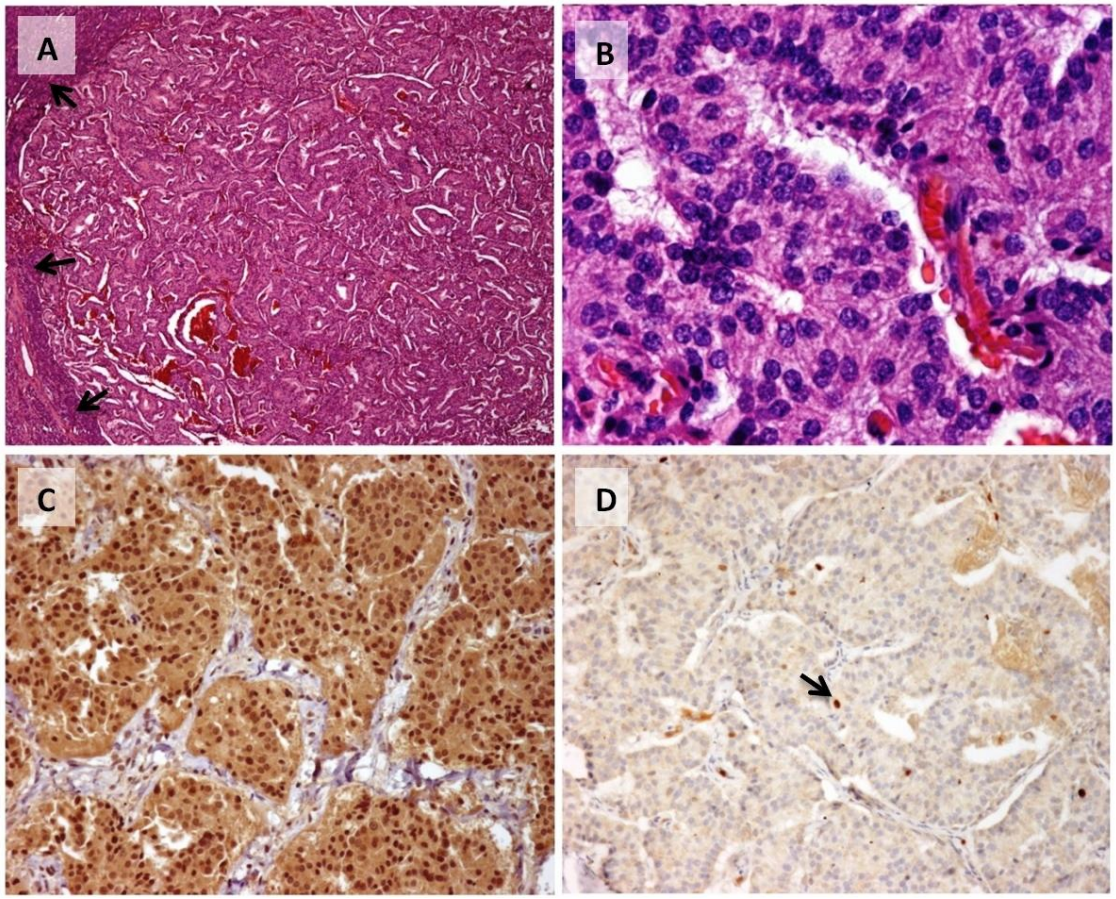

Fig. 2. (A). Hematoxylin and eosin-stained section shows a well-differentiated neuroendocrine tumor of the pancreas with trabecular growth pattern. The tumor is well demarcated from the surrounding normal pancreas (arrows). (B). Salt-and-pepper chromatin. (C). Immunohistochemistry showing insulin-positive expression in neoplastic cells. (D). Low mitotic rate (Ki-67 <1%)

3. DISCUSSION

We present an unusual case displaying the association of PCLD and an insulinoma. The identification of the cause for the hypoglycemia in this clinical case was challenging. A first postulated hypothesis to explain the recurrent hypoglycemic events was low glycogen storage in the context of a patient with chronic liver disease. However, the evaluation of liver function was normal. The features that obliged to rule out a NET in the context of PLD were: 1) an intact

protein synthesis, even in the presence of severe PLD, 2) the absence of cirrhosis, and 3) the known fact that hypoglycemia is not described as a PLD symptom [1,2].

Table 3. Sulfonylureas test

Sulfonylureas inserum	ng/ml
Acetohexamide	Not detected
Chlorpropamide	Not detected
Glimepiride	Not detected
Glipizide	Not detected
Glyburide	Not detected
Nateglinide	Not detected
Repaglinide	Not detected
Tolazamide	Not detected

After documenting the Whipple's triad we started the study of the etiology of the hypoglycemia. We ruled out hormone deficiencies and use of drugs associated with hypoglycemia. In addition, the clinical context was not of a critical illness. The prolonged diagnostic fast indicated endogenous hyperinsulinism by the presence of a glucose concentration less than 55 mg/dl (<3.0 mmol/liter), insulin of at least 3.0 μU/ml (18 pmol/liter), C-peptide of at least 0.6 ng/ml (0.2 nmol/liter), and proinsulin of at least 5.0 pmol/liter [3,4,5]. Also, the screening for sulfonylurea use was negative. At that time, procedures for localizing an insulinoma performing an endoscopic ultrasound and a triphasic CT scan of the pancreas where conducted. After a laparoscopic distal pancreatectomy, definitive diagnosis was an insulinoma with production of both insulin and proinsulin.

The association of PLD and NET is rare. We found two case reports in the literature, both describing a more aggressive presentation. On the first case, a liver NET showed an intermediate grade, with Ki-67 expression of 10-15%, positive for keratin, CD56, and synaptophysin [6]. The second case reported a malignant insulinoma metastatic to the liver, causing biliary obstruction associated with PLD [7].

One of the most interesting features of PCLD is the absence of abnormal liver function. Similarly to our case, usually parenchymal liver volume is preserved and the capacity of the liver to synthesize proteins remains intact. Abnormalities of liver enzymes or total bilirubin are generally absent. In severe PLD, γ-glutamyltransferase and alkaline phosphatase can be elevated.

Finally, there is probably a molecular link between these two entities. The mammalian target of rapamycin (mTOR) has an important role in the regulation of cell growth in response to growth factors. In addition, mTOR is a nutrient sensor and a key regulator of metabolism [8]. In PLD, expression of mTOR is increased in the epithelium that lines the cysts, which suggests that the mTOR pathway might modulate the growth of the liver cysts. Also, mTOR/P70S6K signaling pathway is involved in the tumorigenesis of insulinomas [9]. This suggests that medical therapies such as rapamycin, an inhibitor of mTOR, or a dual PI3K/mTOR inhibitor (NVP-BEZ235) may have a role in the treatment of these conditions [10]. However, in clinical trials the benefits of the inhibition of mTOR by rapamycin have not been fully effective [11].

4. CONCLUSION

In spite a low probability of the coexistence of two unusual conditions, hypoglycemia should always be thoroughly evaluated to rule out treatable conditions.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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