Glycogenic Hepatopathy: Persistent Lactic Acidosis in Poorly Controlled Type 1 Diabetic

Hepatopatia Glicogénica: Acidose Láctica Persistente em Diabético Tipo 1 Mal Controlado

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Abstract:

Mauriac syndrome is a rare complication of poorly controlled type 1 diabetes *mellitus* and remains underdiagnosed. Hepatomegaly is a typical sign and appears in most patients. The clinical signs considered typical of this syndrome (short stature, obesity, and hepatomegaly) are often incomplete, and lactic acidosis can be exacerbated by high-dose insulin and glucose therapy, as occurs during the treatment of diabetic ketoacidosis. Glycogen storage liver disease must be differentiated from metabolic dysfunction-associated steatotic liver disease as a cause of hepatomegaly and liver function abnormalities in patients with type 1 diabetes *mellitus*, as these conditions require different therapeutic approaches and have distinct prognoses.

The authors describe a clinical case of persistent lactic acidosis during a diabetic ketoacidosis episode in a woman with poorly controlled type 1 diabetes, hepatomegaly, and glycogen storage liver disease, which was diagnosed through liver biopsy.

Keywords: Acidosis, Lactic; Diabetes Mellitus, Type 1/complications; Glycogen Storage Disease; Hepatomegaly; Liver Glycogen.

Resumo:

A síndrome de Mauriac é uma complicação rara da diabetes *mellitus* tipo 1 mal controlada e ainda é subdiagnosticada. A hepatomegalia é um sinal típico e aparece na maioria dos doentes. Os sinais clínicos considerados típicos desta síndrome (baixa estatura, obesidade e hepatomegalia) são frequentemente incompletos e a acidose láctica pode ser exacerbada por terapêutica com altas doses de insulina e glicose, como acontece no curso do tratamento da cetoacidose diabética.

A hepatopatia glicogénica deve ser diferenciada da *metabolic dysfunction-associated steatotic liver disease* como causa de hepatomegalia e anormalidades nas funções hepáticas em doentes com diabetes *mellitus* tipo 1, uma vez que ambas exigem abordagens terapêuticas distintas e apresentam prognósticos diferentes.

Os autores descrevem um caso clínico de acidose láctica persistente durante um episódio de cetoacidose diabética numa mulher com diabetes *mellitus* tipo 1 mal controlada, hepatomegalia e hepatopatia glicogénica que foi diagnosticada por biópsia hepática.

Palavras-chave: Acidose Láctica; Diabetes Mellitus Tipo 1/complicações; Doença de Depósito de Glicogénio; Glicogénio Hepático; Hepatomegalia.

Learning Points

1. In patients with poorly controlled T1DM, hepatomegaly with elevated liver enzymes, and persistently elevated plasma lactate levels should raise the suspicion of GH.
2. The differential diagnosis between glucogenic liver disease and MASLD is important, since they have different therapeutic approaches and prognosis.
3. Continuous insulin delivery might be a good choice of treatment of patients with MS, avoiding large variations in blood glucose.

Introduction

First described in 1930, Mauriac syndrome (MS) is typically diagnosed in young patients with poorly controlled type 1 diabetes *mellitus* (T1DM) with grow retardation, delayed puberty, cushingoid features, hypercholesterolemia and hepatomegaly.[1] Glycogenic hepatopathy (GH) can present as the sole clinical manifestation in both adults and children. GH is an underrecognized and uncommon complication of poorly controlled T1DM manifested by hepatomegaly, abdominal pain, nausea, vomiting, elevated serum aminotransferases and hyperlactacidemia.[2,3]

GH develops due to excessive accumulation of glycogen in the hepatocytes, leading to hepatomegaly and liver impairment. In the presence of hyperglycemia, glucose enters hepatocytes by facilitated diffusion. It is then irreversibly

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phosphorylated by the enzyme glucokinase to glucose-6--phosphate and subsequently converted to glycogen by insulin. A history of poorly controlled diabetes, elevated liver enzymes and characteristic histological changes on liver biopsy are diagnostic of GH.[4]

Although liver biopsy using periodic acid-schiff (PAS) is the gold standard for the final diagnosis of GH, it is expected that other non-invasive methods, including the measurement of the serum lactate levels, will become established in the near future for this purpose.[5]

The authors present a rare case of persistent lactic acidosis during an episode of ketoacidosis in a young woman with poorly controlled T1DM, hepatomegaly and glycogenic hepatopathy, which was diagnosed by liver biopsy.

Case Report

A 21-year-old female patient diagnosed with T1DM at the age of 7, revealed by initial diabetic ketoacidosis (DKA), presented to the emergency room (ER) with nausea and vomiting in the last 6 days, describing mild abdominal pain in the last 4 months.

She had a protuberant abdomen, with tenderness over an enlarged liver.

Until the age of 13, she had regular glycemic control, but over the past 8 years, she has experienced multiple emergency admissions due to DKA and recurrent episodes of hypoglycemia, within a challenging family environment and inconsistent insulin therapy.

Despite subcutaneous insulin therapy (basal insulin glargine – 40 U/night and prandial insulin lispro), her glycated hemoglobin (HbA1c) remained persistently above 10%, and she experienced frequent glycemic variability, with episodes of hypoglycemia (without a specific pattern) and reports of hyperglycemia (>300 mg/dL), mainly after meals. Over the past 3 years, she also developed hepatomegaly and persistent elevation of aminotransferases. She had no family history of hepatic disease, alcohol intake or herbal, drug or over-the-counter medication exposure.

A liver biopsy performed at the age of 19 revealed slightly irregular architecture, significant glycogen accumulation, and some glycogenated nuclei, with focal macrovacuolar steatosis observed. She was diagnosed with GH (Fig. 1), but no further treatment or intervention was implemented at that time.

At the ER, she was diagnosed with a new episode of DKA. Blood glucose level was 17.21 mmol/L with metabolic acidosis and increased anion-gap (pH 7.310, pCO2 23.9 mmHg, HCO3- 14.8 mEq/L, anion gap of 20.2 mmol/L) and elevated serum lactate level (6.99 mmol/L). Urine test was positive for ketones (15 mg/dL). During DKA treatment, arterial blood gas assessment revealed persistent lactic acidosis, regardless of insulin and dextrose infusion (Fig. 2).

Laboratory findings revealed a hepatocellular pattern of hepatitis. Autoimmune hepatitis, infectious causes of hepatomegaly, hemochromatosis, and Wilson's disease were ruled out during the evaluation for hepatitis (Table 1).

The ultrasound showed hepatomegaly (20.5 cm), increased liver echogenicity (more hyperechoic compared to the spleen), and a heterogeneous liver texture. The computed tomography (CT) scan demonstrated an enlarged liver measuring 21 cm along the midclavicular line, with normal parenchymal structure and no focal lesions. Additionally, the scan showed no signs of splenomegaly, edema, or ascites (Fig. 3).

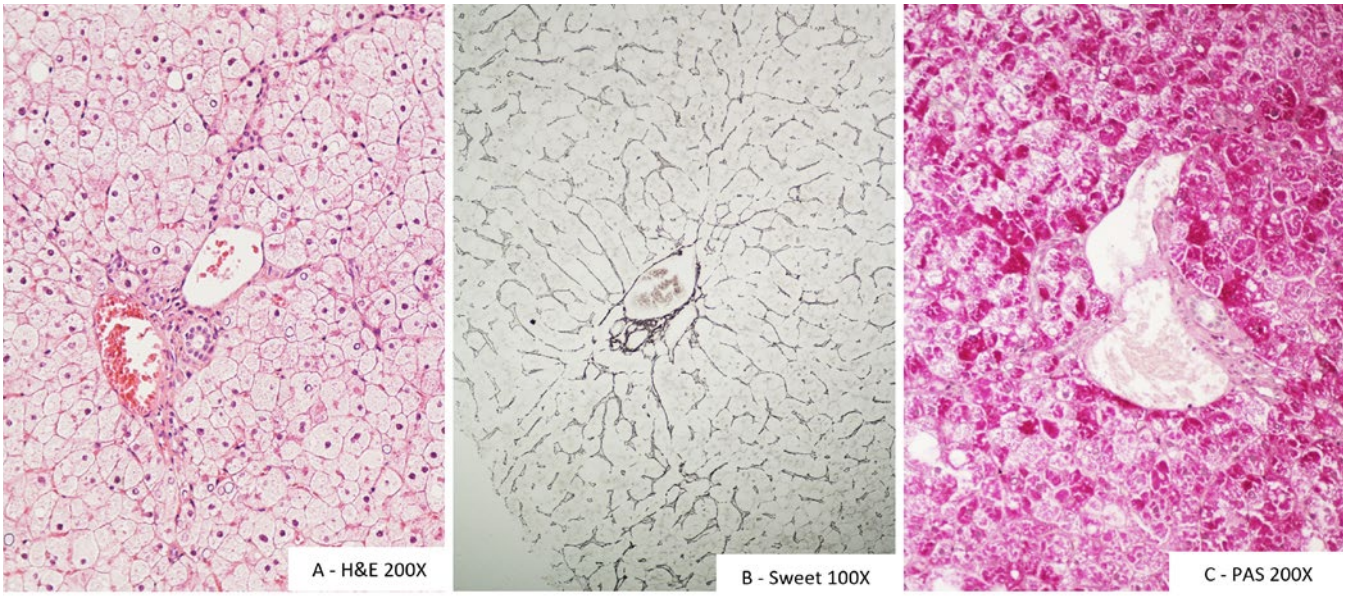

Figure 1: Glycogenic hepatopathy. Regular portal tract and adjacent enlarged and plant-like hepatocytes with focal vacuolated nuclei (**A**). Liver tissue with irregularity in the orientation of the trabeculae (**B**). Increased amounts of glycogen are show with the periodic acid-schiff stain without digestion (**C**).

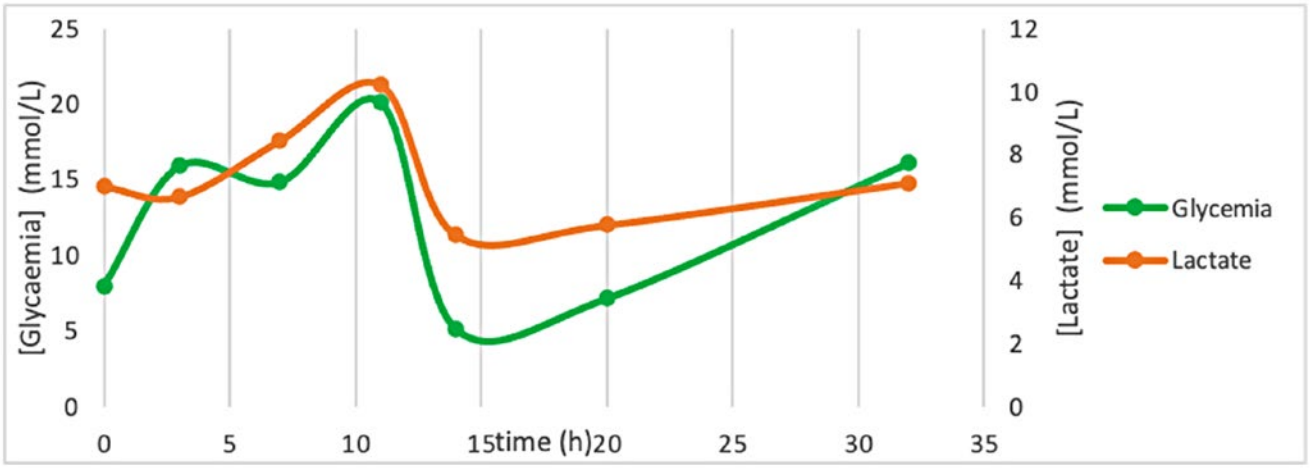

Figure 2: Serial measurements of glycemia and lactate.

Table 1: Laboratory results.

Laboratory analysis	Results	Reference values	Laboratory analysis	Results	Reference values
Coagulation			**Immune serum**	8.2	8.7
PT %	121%	70%-120%	Cortisol	435 nmol/L	138-690 nmol/L
HPT	169%	50%-150%	TSH	1.64 mLU/L	0.4-4.0 mLU/L
Biochemistry			FT3	1.12 ng/dL	2.0-4.4 ng/dL
C reactive protein	0.12 mg/dL	<0.5 mg/dL	FT4	3.4 pg/mL	0.9-2.3 pg/mL
Albumin	3,7 g/dL	3.5-5.0 g/dL	IgA	129 mg/dL	70-400 mg/dL
AST	344 UI/L	10-40 U/L	IgM	41.7 mg/dL	40-230 mg/dL
ALT	380 UI/L	10-55 U/L	IgG	1224.7 mg/dL	700-1600 mg/dL
GGT	418 UI/L	9-48 U/L	Ig-E	579.8 mg/dL	<100 mg/dL
Total serum bilirubin	0.5 mg/dL	0.1-1.2 mg/dL	Anti-mitochondrial antibody	Negative	Negative
LDH	413 U/L	140-280 U/L	HAV-IgM	Negative	Negative
HbA1c	10.4%	4.0%-5.6% (Normal); <7% (Diabetic target)	HBs antigen	Negative	Negative
C-peptide	<0.10 ng/mL	0.5-2.0 ng/mL	HBV-DNA	Negative	Negative
Total cholesterol	139 mg/dL	<200 mg/dL	HCV antibody	Negative	Negative
Triglycerides	188 mg/dL	<150 mg/dL	HCV-RNA	Negative	Negative
HDL	57 mg/dL	>40 mg/dL (men), >50 mg/dL (women)	CMV-IgM	Negative	Negative
LDL	104 mg/dL	<100 mg/dL	EBV-VCA IgM	Negative	Negative
Iron	25 micromol/L	10-30umol/L	EBV-VCA IgG	Negative	Negative
Blood copper levels	93 mg/dL	70-140 ug/dL	EBV-EBNA antibody	Negative	Negative
Ceruloplasmin	42,1 mg/dL	20-60 mg/dL	HIV 1/2	Negative	Negative

ALP: alkaline phosphatase, AST: aspartate transaminase, CMV: cytomegalovirus, EBV: Epstein-Barr virus, FT3: free triiodothyronine, FT4: free thyroxine, GGT: gamma-glutamyl transpeptidase, HAV: human hepatitis A virus, HBV: human hepatitis B virus, HCV: human hepatitis C virus, HDL: high-density lipoprotein, HIV: human immunodeficiency virus, HPT: hepaplastin test, LDH: lactate dehydrogenase, LDL: low-density lipoptrotein, PT: Prothrombin time, TSH: thyroid-stimulating hormone.

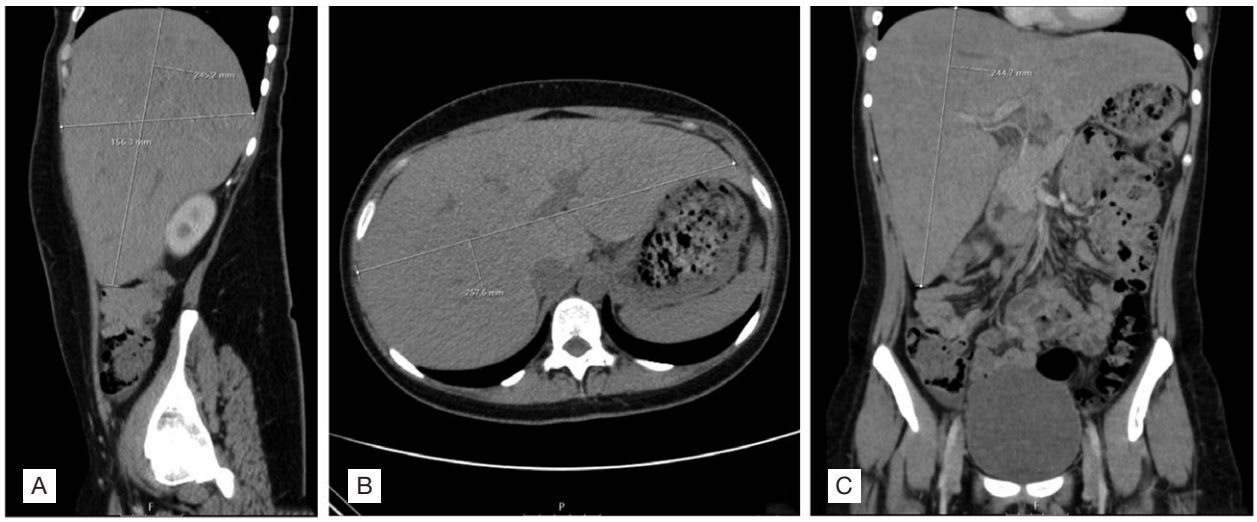

Figure 3: Contrast-enhanced computed tomography scans in the ER showing severe hepatomegaly and fatty liver. **[A, B, C]**.

During hospitalization, she experienced episodes of hypoglycemia, which led to a reduction in her insulin doses. Upon discharge, she was prescribed basal insulin degludec (34 U/night) and prandial insulin lispro, with improved metabolic control, as evidenced by her capillary blood glucose readings remaining within target values.

A diagnosis of Mauriac syndrome (MS) was made based on the presence of long-term decompensated T1DM, hepatomegaly, chronic hepatitis with a hepatocellular pattern and GH on liver biopsy and prolonged lactic acidosis.

The therapeutic approach included extensive re-education and information about the syndrome. The importance of improving compliance with glycemic control and adequate diet was reinforced. After hospital discharge, the patient missed some scheduled appointments and maintains poor adherence to treatment with any family support. She continued to have mild hepatomegaly, along with mild abnormalities in her liver enzymes, and persistently elevated lactate levels (7.3 mmol/L).

Discussion

One of the most important differential diagnoses in our case is metabolic dysfunction-associated steatotic liver disease (MASLD), which is associated with obesity and is more commonly found in patients with type 2 diabetes *mellitus*.[6] Clinically, it can be difficult to distinguish between glycogenic hepatopathy (GH) and MASLD, as both can cause hepatomegaly, elevated liver enzymes, and increased echogenicity on ultrasound. However, GH does not present the typical "fatty liver" pattern seen in MASLD. The definitive diagnosis is made through liver biopsy.[7]

The prognoses of these conditions differ significantly. GH has a more benign clinical course, with the potential for complete resolution once optimal glycemic control is achieved. In contrast, MASLD can progress to metabolic dysfunction-associated steatohepatitis (MASH) in 20%–30% of cases, which increases the risk of cirrhosis and liver cancer.

The patient had persistent elevated lactate levels during and after insulin treatment of DKA. Similar findings were reported by other authors who reported GH.[8] The underlying mechanism remains unclear. GH can be associated with lactic acidosis, particularly following insulin treatment. In DKA, elevated lactate may be associated to glycolysis induced by hyperglycemia and seems to vary according to ketogenesis. Thus, there seems to be a metabolic abnormality in MS that differs from, or occurs in addition to, insulinopenic diabetes.[9]

Lactate is produced from pyruvate as an end product of glycolysis under anaerobic conditions. It is produced in most tissues in the body, but primarily in skeletal muscle, brain, intestine and red blood cells. During stress conditions is also produced in the lungs, white blood cells and splanchnic organs. Most lactate is cleared by the liver, where it is the substrate for gluconeogenesis, and a small amount is cleared by the kidneys.[10] The most common cause of elevated serum lactate is type A, found in pathologies such as cardiogenic, septic and hypovolemic shock, trauma and severe hypoxemia. Type B is less common and arises without evidence of tissue hypoperfusion or shock such as: congenital lactic acidosis, ethanol intoxication, diabetic ketoacidosis, exercise, human immunodeficiency virus infection and treatment, liver disease, malignancy, medication, mitochondrial myopathy, thiamine deficiency, total parental nutrition and trauma.[11,12]

In adults with T1DM, hepatic defects outcoming from MS can be observed without the entire syndromal features. In T1DM with poor glycemic control, two major events occur: hyperglycemia and high-dose insulin administration. Both induce an increased risk for hepatic glycogen overload, causing lactic acidosis. In MS, impaired gluconeogenesis and a defect of pyruvate to glucose conversion could be accounted for lactic acidosis.[8,10]

Most reports demonstrated that adequate management of glucose and daily insulin dose could lead to a complete

remission of clinical, laboratory and histological abnormalities.[5,13,14] The reduction of hepatic enzymes after achieving reasonable glycemic control suggests that liver biopsy and other extensive work-up may be unnecessary in the management of similar patients.[13] A recent review hypothesized that GH could be diagnosed conservatively, and prompts the execution of liver biopsy only in case of doubt about the diagnosis or lack of clinical response.[13]

With this case, the authors aim to highlight the critical importance of distinguishing between GH and MASLD, given their distinct therapeutic approaches and prognoses. In poorly controlled T1DM patients presenting with hepatomegaly, elevated liver enzymes, and persistent hyperlactatemia, GH should be strongly considered. Furthermore, this case underscores the need to prioritize patient adherence to insulin dose adjustments rather than indiscriminate dose escalation in response to hyperglycemia, which may exacerbate lactate elevation. Continuous insulin delivery systems may offer a viable treatment option for managing metabolic instability, minimizing glycemic fluctuations. ■

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MP; MF, JC – Designing, gathering information, writing and revising article
AG, APL – Guiding and revising the article.
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Declaração de Contribuição

MP; MF, JC – Conceção, recolha de informação, redação e revisão do artigo.
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