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Unexplained Persistent Acidosis Post Recovery of Diabetic Ketoacidosis in a Patient with Glycogen Hepatopathy, A Case Report

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Abstract **Case Report**

Glycogenic hepatopathy (GH) is a disorder linked to inappropriate glycemic control attributable to insulin deficiency, intensive insulin therapy for diabetic ketoacidosis (DKA), or excessive glucose administration to control hypoglycemia. Our Case report describes a patient with unexplained persistent acidosis mimicking nonresolving DKA associated with glycogen hepatopathy in an adolescent female with T1DM. Clinical judgment for signs of hepatomegaly, early confirmation of lactic acidosis and a high index of suspicion in the context of uncontrolled T1DM, may be indicative and lead to a timely diagnosis. Additional research is required to develop a noninvasive, rapid diagnostic test to avoid the extensive investigations required to evaluate suspected cases of GH. Clinical probability criteria are required which would be easy to apply so that highly probable GH cases can be managed noninvasively and a liver biopsy should only be performed when the diagnosis is uncertain.

Keywords: Ketoacidosis, glycogen hepatopathy, lactic acidosis, diabetes.

INTRODUCTION

Glycogenic hepatopathy (GH) is a disorder linked to inappropriate glycemic control attributable to insulin deficiency, intensive insulin therapy for diabetic ketoacidosis (DKA), or excessive glucose administration to control hypoglycemia [1], especially in the management of type 1 diabetes mellitus (T1DM). In adolescents with T1DM, excessive hepatic glycogen storage, hepatomegaly, lactic acidosis and elevated transaminases are associated with a rare condition called mauriac syndrome, which may have cushingoid features, delayed puberty and growth failure [2-3].

Lactate is a product of anaerobic glycolysis, which is eventually metabolized to glucose in the hepatocytes. When lactate exceeds the liver cell capacity, hyperlactatemia occurs which frequently progress to lactic acidosis. There are two types of lactic acidosis, type A is mainly attributed to tissue hypoxia, anaerobic glycolysis, or an adrenergic response to stress with type B not related to tissue hypoperfusion but with disorders such as congenital enzyme deficiencies, liver failure, diabetes mellitus and malignancies [3].

The case report describes a patient with persistent acidosis which was found to be hyperlactatemia or lactic acidosis mimicking nonresolving DKA in an adolescent female with T1DM as well as hepatomegaly.

CASE REPORT

The patient is a 16-year-old Saudi female student with a history of T1DM since the age of 9 years. She has a history of multiple admissions due to DKA with the last admission 8 months ago. Her glycosylated hemoglobin (HbA1c) ranged from 12.5-16.4% (Figure

1) since 2010. In the last year, her T1DM was managed with an insulin pump but she decided to revert to the subcutaneous route recently. She also had a history of depression and social problems contributing to her noncompliance. During the current consultation, she complained of a dry cough, sore throat, nausea and abdominal pain for one week. Clinically she manifested with signs of dehydration and had an elevated blood glucose level of 22.4 mmol/L, positive urine ketones, high anion gap of 24 and metabolic acidosis with a pH of 7.29.

She was admitted with a diagnosis of DKA and managed with intravenous fluids, correction of electrolytes, and insulin infusion as per protocol with close glucose monitoring. The next day, she developed a temperature (38.2℃) with tachycardia and tachypnea; her blood pressure remained stable with no other clinical signs of hypoperfusion. An abdomen examination revealed a non-tender hepatomegaly 6 cm below the right costal margin with no splenomegaly, which was confirmed by ultrasonography (US) and computerized tomography (CT) scan (Figure 2 and 3.) The measurement of the liver in its longest axis was 22.1 cm with homogenous echogenicity and without any focal lesions. Her initial liver enzymes were elevated with an Aspartate transaminase (AST) of 170 units/L and Alanine transaminase (ALT) 86 units/L. The results of the liver function tests indicated a total protein of 69 g/L, total bilirubin 2.7 Umol/L, alkaline phosphatase 104 units/L, prothrombin time 12.6 and international normalized ratio (INR) 1.1. An incidental finding was a serum lactate of 9.1 mmol/L with a pH of 7.25 and an anion gap of 18 mmol/L. Serial monitoring of the blood glucose indicated a range of 12 to 20.2 mmol/L (Figure 4) with no ketones in her urine. This persistent high anion gap acidosis with a high lactate required additional investigation to determine the etiology. Initially broad-spectrum antibiotics were prescribed to treat any occult septic source as the cultures were pending.

In the subsequent days, the patient continued to improve, became afebrile and her blood glucose ranged from 8-12 mmol, the anion gap closed to 12, the pH corrected to 7.40 and the carbon dioxide (CO_2)18. The insulin infusion was changed to subcutaneous fixed doses of Glargine and Aspart insulin. The initial investigation for sepsis, as advised by the Infectious Disease Consultant, indicated negative blood cultures. The CT scan of the chest, abdomen and pelvis was normal, as well as the transthoracic echo and Viral Hepatitis Screening and the antibiotics were discontinued.

Due to the persistent high lactate (5.5-6.0 mmol/L), abnormal liver enzymes and hepatomegaly with no obvious cause, further investigation was done for a possible underlying autoimmune or connective tissue disorders with tests like alpha 1 antitrypsin, ceruloplasmin, tissue transglutaminase, antinuclear antibody, anti-double stranded DNA, peripheral anticytoplasmic antibody central anticytoplasmic antibody, antimitochondrial antibodies and anti-smooth muscle antibodies. On the fourth day of admission, the patient was transferred out of the ICU. The pending laboratory tests were negative. We reviewed literature, seeking any association between hepatomegaly, elevated lactate and DKA with a high index of suspicion for Glycogenic Hepatopathy/Mauriac Syndrome. With this differential diagnosis, a liver biopsy was planned.

In the ward, the patient remained stable clinically with normal blood glucose levels but the lactate persisted in the range of 3.3 – 4 mmol/L. The liver enzymes (AST 74, ALT 56) improved. The liver biopsy was performed prior to discharge (Figure 5.) The biopsy report indicated enlarged hepatocytes compressing the sinusoids with preserved architecture (Figure 6). Subsequently after discharge from the hospital patient is being followed regularly in gastroenterology and endocrine clinics and her disease management plan is regularly modified.

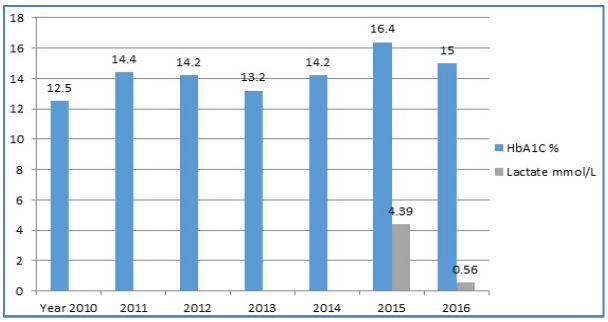

Fig-1: Glycosylated Hemoglobin and Lactic acid trends prior to current admission

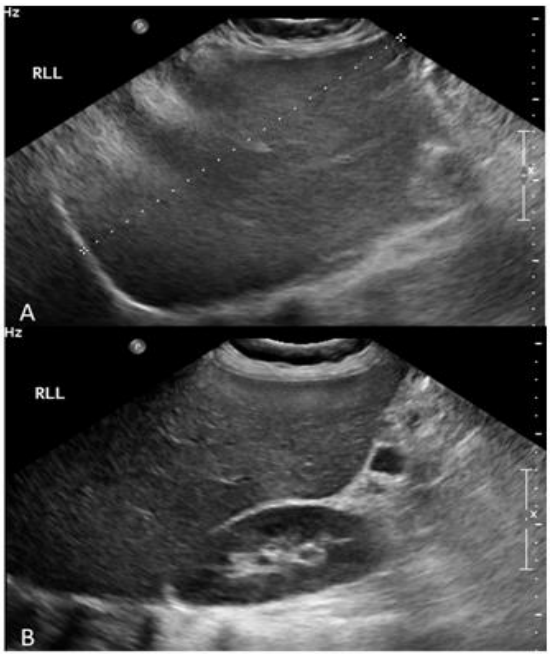

Fig-2: US for the right lobe of the liver along the mid clavicular (A) and mid axillary (B) lines, shows mild hepatomegaly

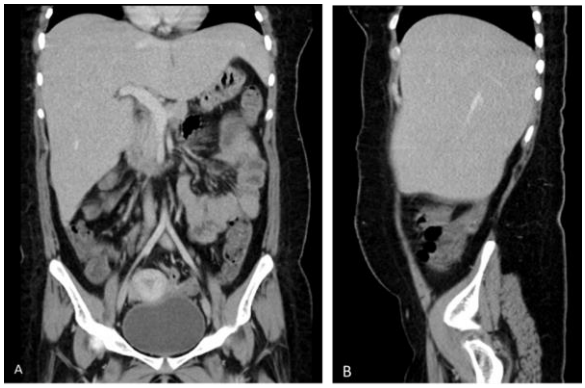

Fig-3: CT for the abdomen and pelvis in Coronal (A) and Sagittal (B) planes, shows mild hepatomegaly

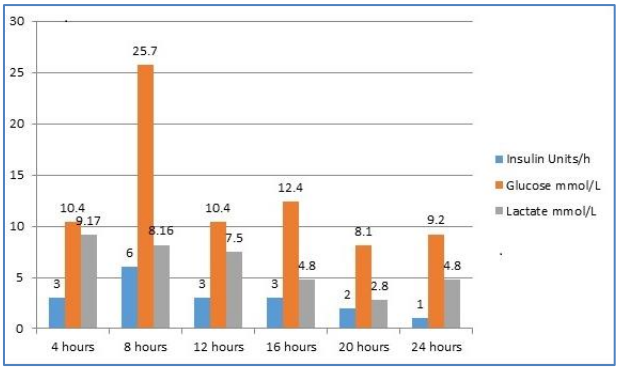

Fig-4: Relationship between insulin, glucose and lactate during 24 hours

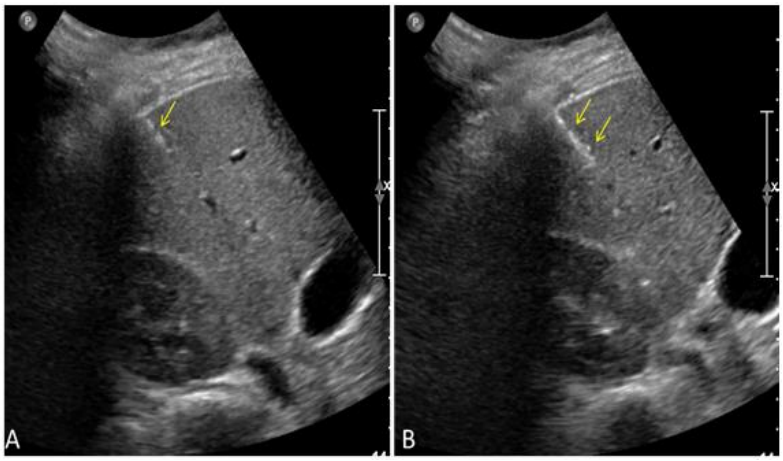

Fig-5: US guided tru-cut biopsy using 18G needle from the right lobe of the liver, yellow arrows. (A) During biopsy needle insertion and (B) after obtaining the soft tissue core

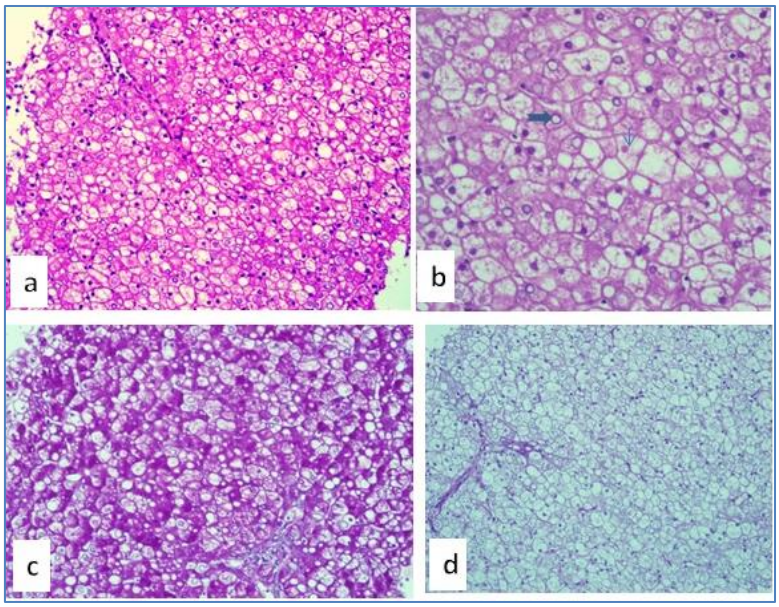

Fig-6: a +b: HE staining x 200, HE staining x 400: the hepatocytes are swollen with pale or eosinophilic cytoplasm and accentuation of the cell membranes. The sinusoids are compressed. Glycogenated nuclei (notched arrow) and mega mitochondria (arrow) are identified c+d: PAS staining, PAS staining with digestion by diastase, showed glycogen accumulation in the hepatocytes

DISCUSSION

Glycogen hepatopathy is a non-inflammatory overload of glycogen in hepatocytes without extra hepatic features of Mauriac syndrome [4]. Mauriac syndrome is a form of GH discovered in 1936, initially in pediatric patients with poorly controlled diabetes presenting with hepatomegaly and endocrine features including growth retardation. In GH, hepatic

glycogenesis occurs mainly due to elevated glucose and insulin levels. Glucose diffuses into the hepatocytes and is converted to glucose-6-phosphate by the enzyme glucokinase. Glucose-6-phosphate is converted to glycogen by the enzyme glycogen synthase. Glycogen synthase exists in an active dephosphorylated form and an inactive phosphorylated form. The active dephosphorylated form of glycogen synthase is produced by the action of a phosphatase enzyme, which is stimulated by elevated glucose and insulin levels. Glycogen is mobilized by glycogen phosphorylase, typically in the post absorptive state. Thus, mechanistically, elevated glucose and insulin levels and decreased glycogen phosphorylase activity in the hepatocyte could lead to deposition of glycogen in hepatocytes.

Most of these patients presented with abdominal pain, hepatomegaly and high HbA1c levels. Adult patients have recurrent DKA, higher AST levels and low albumin compared to pediatric patients with GH [5]. Lactic acidosis is often seen as a complication of GH; the explanation is not clear and most possibly multifactorial. A reduction in gluconeogenesis in the liver may raise lactate levels in the body and the lactic acidosis in Mauriac syndrome could be explained by reduced gluconeogenesis and lack of conversion of pyruvate to glucose [6].

To diagnose GH as a sole condition in such cases, a thorough review and exclusion of other causes of liver disease such as infection, neoplastic, autoimmune, metabolic (glycogen storage disease), nonalcoholic fatty liver disease must be done. These tests were all negative in our patient. Intensive treatment of diabetic ketoacidosis with dextrose and insulin often worsens lactic acidosis, as was experienced in our case [7].

A liver biopsy plays a pivotal role in the diagnosis of GH and Mauriac syndrome. The gold standard features described in literature include marked glycogen accumulation resulting in pale, swollen hepatocytes, no or mild fatty change, no or minimal inflammation, no or minimal spotty lobular necrosis, and an intact architecture with no significant fibrosis [8]. Our biopsy indicated enlarged hepatocytes compressing the sinusoids with preserved architecture. There was no fibrotic or periportal inflammatory changes. There is tendency for recurrent GH with poor blood glucose level control as these patients can also present with predominant cholestasis which can produce liver fibrosis and, finally, liver cirrhosis [9].

The principle of management is mainly supportive with close supervision of HbA1c levels, titration of insulin doses, education and counseling for early recognition and treatment and the prevention of DKA. In previous reports, successful management of GH was seen in pancreatic transplant recipients suggesting the possible reversibility of this condition through the treatment of diabetes [10]. Though this condition is clinically benign, due to its relapsing characteristics as was experienced in the current case, close follow-up is essential especially if glycemic control targets are not achieved. Evidence of severe forms of bridging fibrosis, which progressed to cirrhosis, has been reported in literature [11].

CONCLUSION

Elevated lactate levels in patients with poorly controlled T1DM presenting with DKA, should alert the treating physician to the possibility of an underlying GH. Several cases, which developed lactic acidosis with high doses of insulin and dextrose therapy for ketoacidosis in T1DM, are reported in literature. Additional research is required to develop a noninvasive, rapid diagnostic test to avoid the extensive investigations required to evaluate suspected cases of GH. Compared to other liver diseases associated with DM, GH is a favorable diagnosis due to its benign nature and good prognosis.

Clinical judgment for signs of hepatomegaly, early confirmation of lactic acidosis and a high index of suspicion in the context of uncontrolled T1DM, may be indicative and lead to a timely diagnosis. Clinically-based probability criteria are required. Such criteria would be easy to apply to the routine clinical and laboratory findings so that highly probable GH cases can be managed noninvasively and a liver biopsy should only be performed when the diagnosis is uncertain.

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