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Case Report

Hepatomegaly in an Adult With Type 1 Diabetes Mellitus: Mauriac Syndrome Still Exists in a Developed Country

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Abstract

We report a case of a 19-year-old male with type 1 diabetes mellitus (T1DM) diagnosed at age 2 years, childhood growth retardation, and multiple admissions for diabetic ketoacidosis, presenting with hepatomegaly and elevated liver transaminase. His hemoglobin A1c (HbA1c) was 13.1% (reference range, < 5.7%). Massive hepatomegaly without splenomegaly was noted and accompanied by significant liver enzyme derangement, and lactatemia. Extensive viral, serologic, genetic, and metabolic tests to identify the etiology of hepatomegaly were unrevealing. A liver biopsy showed microvesicular and macrovesicular steatosis with periportal and lobular inflammation consistent with glycogenic hepatopathy (GH) of Mauriac syndrome. A continuous subcutaneous insulin infusion therapy was initiated and gradually titrated. With an improvement in HbA1c down to 9.2% over 9 months, liver transaminase levels became normalized. The current report includes a thorough evaluation of causes of hepatomegaly in an adult with T1DM and highlights the importance of glycemic control in ameliorating GH.

Key Words: Mauriac syndrome, type 1 diabetes mellitus, glycogenic hepatopathy, hyperglycemia

Abbreviations: BMI, body mass index; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; DKA, diabetic ketoacidosis; DM, diabetes mellitus; GH, glycogenic hepatopathy; HbA1c, glycated hemoglobin; MASLD, metabolic dysfunction–associated steatotic liver disease; MS, Mauriac syndrome; T1DM, type 1 diabetes mellitus.

Introduction

Mauriac syndrome (MS) is a rare complication of poorly controlled type 1 diabetes mellitus (T1DM) and, rarely, type 2 diabetes mellitus. It is characterized by stunted growth and development, cushingoid features, and its characteristic feature of hepatomegaly caused by excess glycogen accumulation in hepatocytes or glycogenic hepatopathy (GH) [1, 2]. GH associated with MS occurs predominantly in the pediatric population and in underdeveloped countries [2]. GH is underrecognized as a cause of liver chemistry abnormalities by adult endocrinologists as it can easily be misdiagnosed as metabolic dysfunction–associated steatotic liver disease (MASLD), a more common hepatic comorbidity in adults with diabetes mellitus (DM). However, the distinguishing GH from MASLD and other causes of hepatopathy is important as the former is reversible with glycemic control [3] while the latter can progress to serious complications such as liver cirrhosis [4]. The current report includes a thorough evaluation of causes of hepatomegaly in an adult with T1DM and highlights the importance of glycemic control in ameliorating GH.

Case Presentation

A 19-year-old male with a history of T1DM diagnosed at age 2 years, a history of childhood growth retardation, and dyslipidemia was referred to the adult endocrinology clinic after being admitted twice for diabetic ketoacidosis (DKA) within one month with a recent hemoglobin A1c (HbA1c) of 13.1% (reference range, < 5.7%). He endorsed adherence to a home insulin regimen consisting of insulin glargine 54 units daily and insulin aspart at 1 unit for every 5 grams of carbohydrate with each meal. However, his glycemic control had been difficult, with morning hyperglycemia of often above 600 mg/dL (70-100 mg/dL) (33.3 mmol/L, 3.9-5.55 mmol/L) and then falling under 50 mg/dL (2.8 mmol/L). He had presented with DKA on 4 occasions over the past 1 year. He reported a history of childhood growth retardation diagnosed at age 5 years for which he had been on growth hormone therapy between age 5 and 13 years. Details regarding growth hormone therapy were not available, as it was managed in a different city and as he was adopted, his parental medical histories were unknown. His weight was 59.5 kg (14th percentile, Z score of −1.07) and height was 1.675 cm (10th percentile, Z score of −1.28) with body mass index (BMI) for age of 30th percentile (Z score of −0.53) (Source: US Centers for Disease Control and Prevention (CDC): Boys, 2-20 Years). His growth chart was reviewed, revealing between 4th and 50th percentile for weight, the 5th and 38th percentile for height, and the 9th and 68th percentile for BMI at age during age 11 to 20 years (Fig. 1).

There was significant hepatomegaly with the liver edge expanding below the level of the umbilicus on the right and

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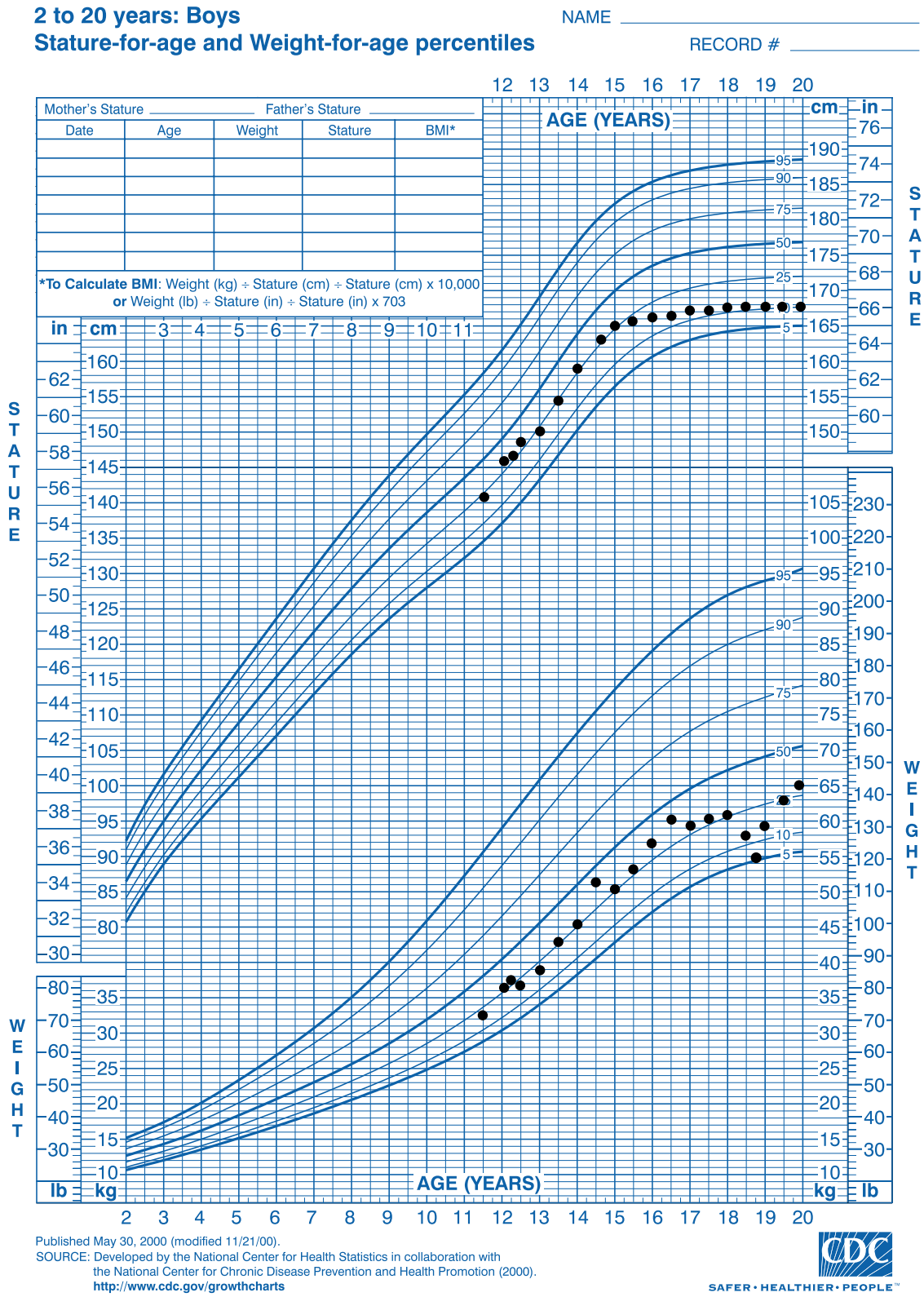

Figure 1. Stature- and weight-for-age percentiles between age 11 and 20 years. (Source: US Centers for Disease Control and Prevention (CDC): Boys, 2-20 Years).

palpable below the left costal margin. The abdomen was soft and nontender. No jaundice, splenomegaly, or ascites were noted. His fundus examination showed background diabetic retinopathy. The rest of the physical examination was unremarkable.

Diagnostic Assessment

Abdominal ultrasound and computed tomography scan confirmed marked hepatomegaly (medial-lateral, cranio-caudal, anterior-posterior dimensions of 27.8, 26.1, and 16.0 cm, respectively) (15.8-24.6, 13.6-21.2, and 12.6-19.8 cm,

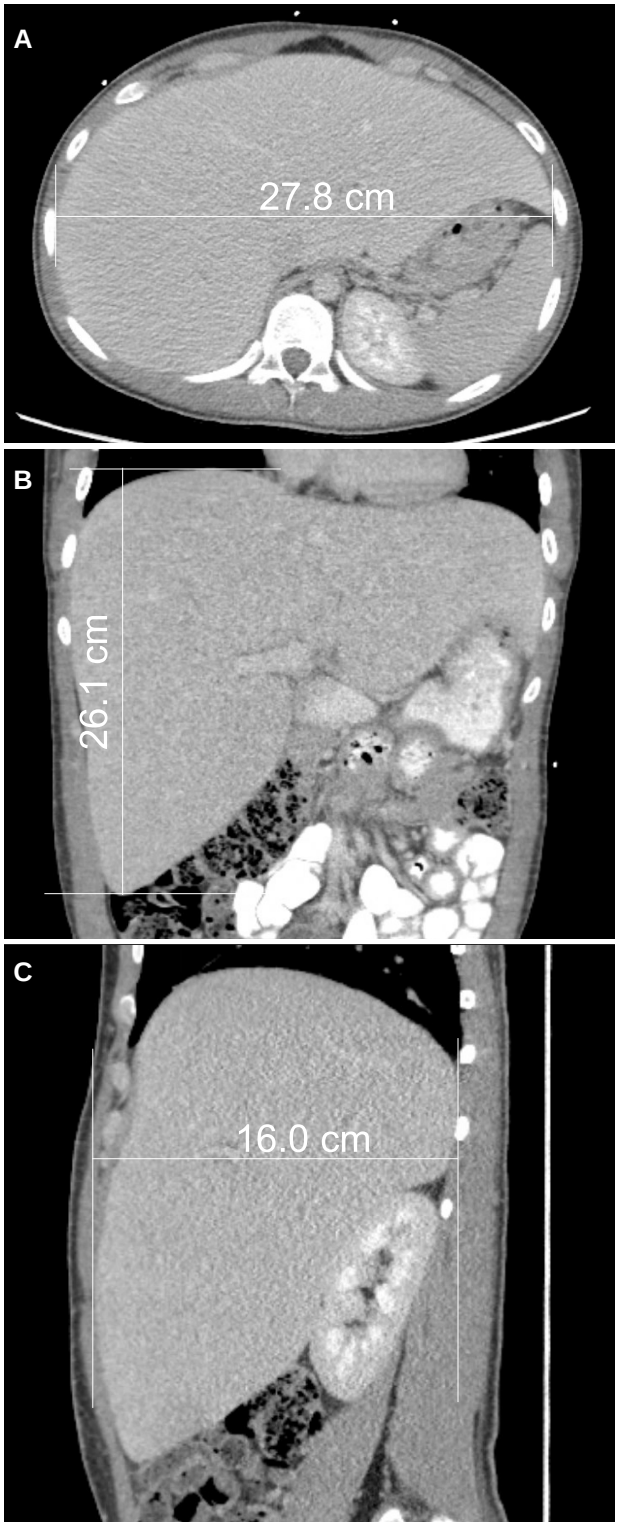

Figure 2. Measurement of liver dimensions based on the abdominal computed tomography sectional images in medial-lateral (A), cranio-caudal (B), and anterior-posterior (C) direction.

respectively [5]) with patent hepatic vasculatures and no fat infiltration (Fig. 2). There was no discrete hepatic mass, biliary ductal dilatation, or splenomegaly.

Complete blood counts revealed hemoglobulin of 14.8 g/dL (13-17 g/dL) (148 g/L, 130-170 g/L), white blood cells of 6.9×10^9/L ($4\text{-}11 \times 10^9$/L), and platelets of 297×10^9/L ($150\text{-}450 \times 10^9$/L). The electrolytes, and thyroid panel were normal. Lipid profile showed a total cholesterol of 161 mg/dL (150-200 mg/dL) (4.16 mmol/L, 3.88-5.17 mmol/L), low-density lipoprotein cholesterol of 90 mg/dL (<130 mg/dL) (2.32 mmol/L, < 3.36 mmol/L), triglycerides of 489 mg/dL (27-150 mg/dL) (5.52 mmol/L, 0.31-1.69 mmol/L), and high-density lipoprotein cholesterol of 25 mg/dL (>39 mg/dL) (0.64 mmol/L, > 1.01 mmol/L). The liver profile revealed markedly elevated alanine transaminase (ALT) of 261 U/L (0-40 U/L), and aspartate aminotransferase (AST) of 565 U/L (0-41 U/L), but normal alkaline phosphatase (ALP) of 106 U/L (39-130 U/L), and normal total bilirubin of 0.4 mg/dL (0.3-1.2 mg/dL) (6.84 µmol/L, 5.13-20.52 µmol/L). Lactate was elevated at 5.9 mmol/L (0.4-2 mmol/L).

T1DM-associated antibodies including glutamic acid decarboxylase 65, insulinoma-associated protein 2, and Zinc transporter 8 antibodies were all negative. Early age of onset for DM at age 2 years, negative T1DM-associated antibodies, delayed childhood growth, hepatomegaly, and his younger biological sister with mild hyperglycemia but no need of insulin prompted referral to the genetics clinic for further investigations of monogenic diabetes and other genetic metabolic syndrome. Genetic tests including glucokinase (*GCK*), hepatocyte nuclear factor (HNF)-1-alpha (*HNF1A*), HNF-1-beta (*HNF1B*), and HNF-4-alpha (*HNF4A*) were negative. Other metabolic panels, including amino acids, organic acid, and acylcarnitine profiles were all normal.

The constellation of uncontrolled T1DM, history of delayed growth, hepatomegaly, and hepatocellular damage was consistent with the diagnosis of Mauriac syndrome (MS). However, the combination of hepatomegaly and markedly elevated liver enzymes prompted consideration of alternative diagnoses. Laboratory tests were unremarkable for acute and chronic viral hepatitis antibodies, ceruloplasmin, antinuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, iron levels, and alpha-1 antitrypsin deficiency. The liver biopsy showed diffusely swollen hepatocytes, scant portal inflammation, and foci of lobular inflammation, macrovesicular and microvesicular steatosis (<10%), and scant periportal fibrosis (Fig. 3). Staining for iron and copper deposits was negative. The pathology result was consistent with either GH or glycogen storage disease types 6 to 12. However, the absence of persistent neonatal hypoglycemia (as occurs in glycogen storage diseases) [6] and a history of poorly controlled brittle diabetes strongly favored the diagnosis of GH associated with MS.

Treatment

During follow-up, his diabetes management was challenging, especially in the context of significant recurrent morning hyperglycemia and daytime hypoglycemia. The continuous glucose monitoring (CGM) data of a representative day while on multiple daily insulin injections are shown in Fig. 4A (DEXCOM® G6, Dexcom, Inc., San Diego, CA, USA). His severe morning hyperglycemia led us to start insulin neutral protamine Hagedorn (NPH) at bedtime in addition to insulin glargine, which resulted in a moderate improvement in morning glucose levels. Eventually, a continuous subcutaneous insulin infusion (CSII) t:Slim X2 (Tandem Diabetes Care Inc., San Diego, CA, USA) with CGM system was implemented. The CGM data of a typical day are shown in Fig. 4B, revealing improvement of morning glycemic control by increased automated basal insulin

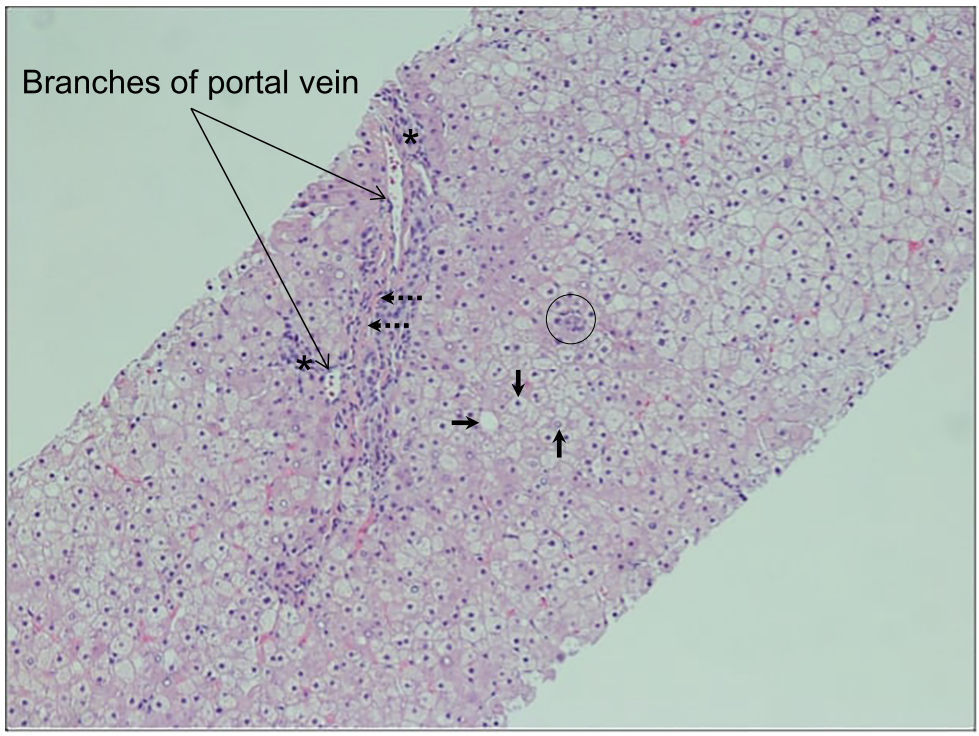

Figure 3. Hematoxylin & eosin stain of percutaneous liver biopsy shows diffusely swollen hepatocytes, scant portal inflammation (asterisk), and foci of lobular (within circle) inflammation, macrovesicular (rightward arrow) and microvesicular (downward arrow) steatosis, prominent glycogenated nucleus (upward arrow), and scant periportal fibrosis (dotted black arrow).

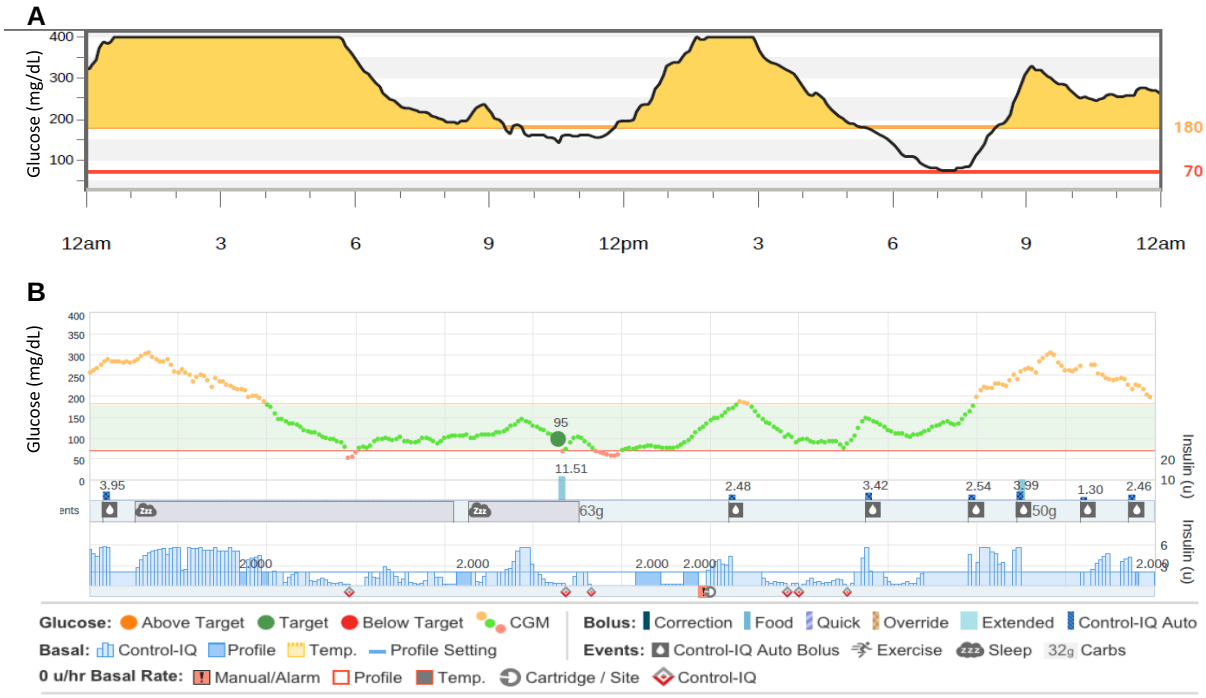

Figure 4. The continuous glucose monitoring (CGM) (DEXCOM® G6, Dexcom, Inc., San Diego, CA, USA) data are shown (A) for a representative day while on multiple daily insulin injections around the time of initial presentation and (B) for a representative day while using a continuous subcutaneous insulin infusion (CSII) t:Slim X2 (Tandem Diabetes Care Inc., San Diego, CA, USA) with CGM about 9 months later. To covert glucose level to mmol/L, divide glucose in mg/dL by 18.

infusion rate overnight. The 30-day average total daily dose of insulin was 100.43 units/day with average CGM reading of 184 mg/dL (10.2 mmol/L), and % in target range (70-180 mg/dL, 3.9-10 mmol/L) of 58%.

Outcome and Follow-Up

Changes of HbA1c, liver enzymes and lactate are shown in Table 1. His HbA1c improved to 9.2% over 9 months. Repeat liver function tests became normal, indicating

Table 1. Changes of HbA1c, liver enzymes, and lactate throughout the follow-up period

Test (reference range)	Initial presentation	~2 months	~4 months	~9 months
HbA1c (<5.7%)	13.1%	12.9%	11.2%	9.2%
ALT (0-40 IU/L)	261 IU/L	103 IU/L	25 IU/L	18 IU/L
AST (0-41 IU/L)	565 IU/L	191 IU/L	29 IU/L	17 IU/L
ALP (39-130 U/L)	106 IU/L	115 IU/L	99 IU/L	112 IU/L
Lactate (0.4-2.0 mmol/L)	5.9 mmol/L, 7.3 mmol/L	No data	3.8 mmol/L	2.3 mmol/L

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA1c, hemoglobin A1c.

resolution of hepatic inflammation, and physical examination revealed resolution of hepatomegaly. Lactate level also gradually decreased from a maximum of 7.3 to 2.3 mmol/L.

Discussion

MS was first described by the French physician Pierre Mauriac in 1930 [7], characterized by stunted growth and development, cushingoid features, and hepatomegaly [1, 2]. One of the intriguing features of MS is reversible hepatomegaly and liver enzyme elevation due to GH in patients with poorly controlled T1DM, predominantly found in the pediatric population and in underdeveloped countries [2]. With the advent of newer insulin analogues and CSII, the incidence of GH has decreased dramatically [8]. However, the recent pooled analysis of 131 studies consisting of 192 patients with T1DM and biopsy-proven GH between 1980 and 2020 showed that 44 studies were reported from USA, 15 from Japan, 10 from UK, 10 from Spain, 6 from South Korea, and 46 were from other countries. However, authors noted a potential selection bias due to favoring liver biopsy in patients with severe liver enzyme elevations and excluding 35 patients due to lack of histopathologic diagnosis [3].

GH usually occurs in patients with significant glycemic variability and using a large amount of insulin to correct hyperglycemia [2]. It is well-known that frequent episodes of DKA are a risk factor for the development of GH [1]. It was postulated that during severe hyperglycemia glucose passes through the glucose transporter 2 and glucokinase facilitates phosphorylation of glucose to glucose-6-phosphate, trapping it inside hepatocytes. Then, glucose-6-phosphate is converted to glycogen by glycogen synthase. The administration of insulin and the simultaneous hyperglycemia activate the enzyme phosphatase, which converts glycogen synthase to its activated dephosphorylated form. The repeated cycles of uncontrolled hyperglycemia and aberrant insulin use lead to accumulation of glycogen within hepatocytes, eventually resulting in hepatomegaly and hepatic enzyme derangement [1, 2]. However, as uncontrolled DM and frequent DKA do not always lead to hepatomegaly, it raises the suspicion of one or more underlying enzyme defects. A possible pathogenesis of the disease was reported by MacDonald et al with a mutation found in phosphorylase kinase catalytic subunit gamma 2 (*PHKG2*) [9]. This enzyme complex activates glycogen phosphorylase that catalyzes the first step of glycogen degradation in the liver. Expression of this mutant enzyme inhibited the activity of the phosphokinase complex and increased glycogen levels. This mutation, in conjunction with uncontrolled hyperglycemia, may further exacerbate hepatic glycogen accumulation [1, 2, 9].

The differential diagnoses should include glycogen storage diseases, MASLD, autoimmune conditions, metabolic, and obstructive diseases. Recognizing GH among other causes of hepatopathy in T1DM is important, as the former is reversible with glycemic control [3], while others lead to serious complications and require different management approaches. It is known that transaminases improve rapidly in most patients with GH associated with T1DM after glycemic control with a median of 3 months [3]. The same study suggested that drastic improvement or normalization of weekly follow-up liver chemistries after glycemic control would be confirmatory of GH and potentially avoid the need of liver biopsy [3].

Our patient had elevated lactate levels during the follow-up period, even when he was not in DKA or acute illness. In a series of 31 children with MS, about half had elevated lactate levels though there were no signs of acute illness, liver failure, sepsis, or DKA [10]. Although the mechanism is not well understood, one of the possible mechanisms could be decreased gluconeogenesis and impaired conversion of pyruvate to glucose [9]. This increased pyruvate level may serve as a substate for the formation of lactate.

It is worth discussing the dawn phenomenon which was conspicuous in the present case. The dawn phenomenon is thought to be caused by the secretion of counterregulatory hormones, such as growth hormone, which in turn leads to increased endogenous glucose production and insulin resistance in the early morning [11]. To address this, understanding the diurnal variation of ambulatory glucose profile using CGM system and individualized basal insulin profiles are of paramount importance [12].

In summary, the current case illustrates liver chemistry disturbance and hepatomegaly caused by GH associated with T1DM. It highlights the importance of recognizing GH and of glycemic control for its management given its reversible nature among causes of hepatopathy in patients with T1DM.

Learning Points

- Despite the overall improvement in glycemic control with the use of newer insulin analogues and the introduction of CSII, cases of MS in T1DM are still found worldwide, even in developed countries.
- Although it is more common in the pediatric population, adult endocrinologists and primary care physicians must consider GH as one of the differential diagnoses for hepatopathy in adult patients with T1DM.
- Glycemic control will result in rapid resolution of liver enzyme abnormalities and hepatomegaly caused by GH in patients with T1DM.

Contributors

All authors made individual contributions to authorship. K.F.: collected data for case writing, did the literature review, and contributed to manuscript writing. Y.S.: histopathology section and preparation of histology images. J.Y.J.: contributed to manuscript writing and reviewed the final manuscript before submission. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent could not be obtained from the patient or a proxy but has been approved by the treating institution.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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