Case Report:

A 21-Year-Old Woman with Hepatomegaly

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About the Authors

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Summary

We report the case of a 21-year old woman with uncontrolled diabetes mellitus type 1 presenting with tender hepatomegaly and mildly elevated liver enzymes, with negative investigations for common causes. She was diagnosed by liver biopsy with glycogenic hepatopathy, an uncommon and likely under-recognized complication of poor glycemic control. The disease is typically reversible after weeks to months of appropriate insulin therapy and is unlikely to lead to permanent liver disease. Our patient was treated with a new insulin regimen and analgesics and discharged home. Unfortunately, on follow-up imaging in our patient 10 months later, her hepatomegaly persists. Her glycemic control remains unchanged and she has since been admitted to hospital twice for episodes of diabetic ketoacidosis.

Résumé

Il s'agit du cas d'une femme de 21 ans présentant un diabète de type 1 non équilibré accompagné d'une hépatomégalie douloureuse et d'une légère augmentation du taux des enzymes du foie, et pour qui les investigations du côté des causes courantes s'avèrent négatives. Une biopsie du foie mena à un diagnostic d'hépatopathie glycogénique, une complication peu courante et souvent mal identifiée qui résulte d'un mauvais contrôle de la glycémie. La maladie est habituellement réversible en quelques semaines ou mois d'insulinothérapie et mène rarement à des atteintes hépatiques permanentes. La patiente a été traitée à l'aide d'une nouvelle insulinothérapie et des analgésiques et a pu retourner à la maison. Malheureusement, lors de l'imagerie médicale de suivi effectuée sur la patiente dix mois plus tard, l'hépatomégalie est toujours présente. La glycémie s'avère inchangée et depuis ce suivi la patiente a dû être hospitalisée deux fois pour des épisodes d'acidocétose diabétique.

Case Presentation

A 21 year-old woman with type 1 diabetes, diagnosed at seven years of age, initially presented to the emergency department (ED) with a two-week history of nausea, vomiting, right upper quadrant (RUQ) abdominal pain and distension, but no documented history of hepatomegaly on physical examination. The patient's medical history was significant for two episodes of diabetic ketoacidosis (DKA) (at age 16 years and three months prior to presentation), suboptimal control of her diabetes (A1C ranging from 12.0–14.3% [normal is 4.6–6.3%] over the preceding two years), and gastro-esophageal reflux. Her only medications were a proton pump inhibitor and rapid-acting insulin (30–40 units), which she administered daily in 4–5 divided doses. She had discontinued her insulin pump months prior and did not use basal insulin. Her vitals were stable and her physical examination was remarkable for RUQ tenderness on palpation. Laboratory investigations showed a glucose level of 9.4 mmol/L, a leukocyte count of 12.4×10^9 (normal being $4.5\text{--}11.0 \times 10^9$) cells/L, a platelet count of 390×10^9 (normal being $150\text{--}350 \times 10^9$). The patient's alanine aminotransferase (ALT) concentration was 113 (normal 14–54) U/L, aspartate aminotransferase (AST) was 98 (normal 15–41) U/L, alkaline phosphatase (ALP) was 103 (normal 32–92) U/L and gamma-glutamyl transpeptidase (GGT) was 70 (normal 5–50) U/L. Her hemoglobin, electrolytes, creatinine, direct and total bilirubin, lipase, international normalized

ratio, partial thromboplastin time, and albumin were normal. An abdominal ultrasound revealed an enlarged liver measuring 23 cm in its maximum craniocaudal dimension. Initial work up for hepatitis was negative, including serum testing for Hepatitis A, B, C and Epstein Barr Virus. She was tentatively diagnosed with hepatitis not yet diagnosed and discharged home to follow up with her family physician.

She returned to the ED four weeks later with worsening RUQ pain, nausea, vomiting, and anorexia. Additional signs and symptoms included hot flashes, pale stools, early satiety, weight loss (approximately 4.5 kg over 4 weeks), and irregular menstrual periods. She denied infectious symptoms or overt signs of bleeding. She had no risk factors for liver disease, such as intravenous drug use, unprotected sex, or alcohol misuse.

On examination, the patient was 167.6 cm tall and weighed 66 kg (body mass index 23.5 kg/m²). She had abdominal distension, with some voluntary guarding in the RUQ, and hepatomegaly, with the liver edge palpable 7–10 cm below the right costal margin. There were no stigmata of chronic liver disease. Repeat laboratory investigations showed increase in her liver enzymes (AST 177 U/L, ALT 299 U/L, ALP 121 U/L, and GGT 169). She was admitted to the internal medicine service for pain control and further work up. A computed tomography (CT) scan of her abdomen showed further enlargement of the liver to 28 cm in length, extending inferiorly to the right iliac fossa (Figure 1).

Figure 1. (A) Coronal and (B) Sagittal views of the patient's abdomen by computed tomography (CT) scan demonstrating marked hepatomegaly.

Figure 2. Pathological slide from percutaneous fine needle aspirate of liver. (A) Swollen hepatocytes with clear cytoplasm, accentuated cell borders and large fat droplets in keeping with co-existing macrovesicular steatosis (200X). (B) Hepatocytes containing megamitochondria that are round to globoid in shape (arrows, 400X).

Additional laboratory testing ruled out Wilson's disease, alpha-1 antitrypsin deficiency, and hemochromatosis. She had poor glycemic control due to a limited ability to afford insulin therapy. She had been admitted for DKA 3 months' prior, and there had been no mention of hepatomegaly. As other causes of hepatitis were ruled out, the clinical presentation in the context of poorly controlled Type 1 diabetes suggested glycogenic hepatopathy. The gastroenterology service was consulted and performed a percutaneous liver biopsy. Pathology (Figure 2) revealed extensive swollen hepatocytes with accentuated cell borders, clear cytoplasm, glycogenic nuclei, and occasional megamitochondria consistent with glycogenic hepatopathy. In addition, mild to moderate macrovesicular steatosis (less than 40%) was also present, suggestive of co-existing non-alcoholic fatty liver disease (NAFLD). However, features of steatohepatitis such as ballooning degeneration, mallory hyaline, or sinusoidal fibrosis were not seen.

In hospital, the patient was seen by the diabetic case

manager and with improved blood glucose control, her RUQ pain¹ improved significantly over the course of a week. She was discharged home with follow-up arranged with endocrinology and hepatology services. Under the management of an endocrinologist, she was prescribed twice daily insulin glargine in addition to mealtime insulin glulisine based on carbohydrate intake; however, her hemoglobin A1C did not improve under this regimen. Upon reassessment by the hepatology service eight months post-discharge, she was found to have no palpable hepatomegaly, with slight improvement in her hepatomegaly by CT scan ten months post-discharge. Unfortunately, she was admitted for DKA on two further occasions after her diagnosis of glycogenic hepatopathy.

Discussion

Glycogenic hepatopathy is a rare but important differential diagnosis for hepatomegaly and transaminitis in patients with diabetes mellitus. It was initially described by Mauriac in 1930 as part of Mauriac's syndrome, which was characterized by uncontrolled diabetes, dwarfism, hypercholesterolemia, cushinoid features, delayed sexual maturity, and hepatomegaly¹; however, it can occur without any associated findings. In most types of cells, glucose entry is insulin dependent. But in the liver, glucose can enter through facilitated diffusion independent of insulin. Once it enters and converts into glucose-6-phosphate by glucokinase, it is trapped inside the cell. Glucose-6-phosphate is then used to form glycogen by the enzyme phosphatase, which is dependent on glucose and insulin. Thus, patients who have poorly controlled diabetes with hyperglycemia and intermittent insulin usage promote entry of glucose into cells and subsequent polymerization into glycogen.^{2,3} Even after insulin levels decline, glycogen production persists, leading to glycogen accumulation in the liver.

Clinical Manifestations

As there are only a few case reports and case series on glycogenic hepatopathy, the prevalence is unknown.⁴ Clinical manifestations are variable. One review of 42 patients with glycogenic hepatopathy identified that 92% of patients had hepatomegaly, 95% had either mild or strong transaminitis, and 72% had an increase in alkaline phosphatase.⁵ Other clinical manifestations include abdominal pain and obstructive symptoms, such as early satiety, nausea, and vomiting. Occasionally there have been reports of ascites, but synthetic liver function is usually normal.² Glycogenic hepatopathy usually occurs in type I diabetes, but can sometimes occur in type II diabetes. It has also been reported in association with short-term high-dose steroid therapy.³

Diagnosis

The most common cause of hepatomegaly in patients with diabetes mellitus is NAFLD, which can occur in over 80% of patients with diabetes and hepatomegaly.⁶ NAFLD is more commonly associated with type 2 diabetes than type 1, and as previously mentioned, glycogenic hepatopathy is more common in type 1 diabetes. Other causes of liver disease, such as viral, autoimmune, and infiltrative diseases should be ruled out before assuming the diagnosis is due to glycogenic hepatopathy.^{4,7}

Unfortunately, glycogenic hepatopathy cannot be distinguished from NAFLD on ultrasound or clinical presentation,⁷ as NAFLD can also present with right upper quadrant pain and dullness, as well as mild to moderate hepatomegaly. Typically patients with NAFLD also have other parts of the metabolic syndrome, including obesity, type 2 diabetes, and hyperlipidemia, and are often asymptomatic.⁸ The only way to differentiate between NAFLD and glycogenic hepatopathy is through a liver biopsy. The usual histological appearance of glycogenic hepatopathy is of pale hepatocytes with compression of sinusoids, glycogenated nuclei, and giant mitochondria.^{2,7} Interestingly, our patient had evidence of both glycogenic hepatopathy and mild to moderate NAFLD. However, one would expect severe steatosis or steatohepatitis on her liver biopsy given her significant hepatomegaly and pain. The clinical manifestations, pathological features and prompt resolution of her symptoms by administration of insulin support that glycogenic hepatopathy was the major underlying cause of her illness.

Treatment and Prognosis

The basis of treatment for glycogenic hepatopathy is optimizing serum glucose control, as identified in several case series and reports describing prompt resolution of tender hepatomegaly and eventual resolution of elevated liver enzymes upon adequate insulin therapy.^{4,5,11,12} The disappearance of clinical hepatomegaly and resolution of symptoms after initiation of insulin can range from weeks to months.^{2,9,10} Improvement or normalization of serum markers may occur several months later.¹¹

In two cases of recurrent glycogenic hepatopathy, or in which achieving optimal glucose targets posed substantial risk of hypoglycemia, pancreatic transplant resulted in resolution of hepatomegaly and of glycogenic hepatopathy.¹² Published case reports lack prolonged follow-up, yet the reported resolution would suggest there are no long-term complications associated with the diagnosis. Since our patient has not been able to achieve glycemic control, her glycogenic hepatopathy

persists. Long-term data and prognosis of untreated glycogenic hepatopathy are not available in the current literature. NAFLD without evidence of non-alcoholic steatohepatitis (as in her case) is usually a relatively benign condition but can progress to fibrosis and cirrhosis.⁸

Conclusion

Glycogenic hepatopathy is an under-recognized clinical entity that should be suspected in patients with tender hepatomegaly in the setting of diabetes mellitus. It is radiographically indistinguishable from NAFLD, and liver biopsy is required for definitive diagnosis. Some authors suggest a trial of four weeks of optimal glycemic control and assessment for resolution of hepatomegaly is a reasonable approach in pediatric diabetic patients once other serum-based etiologies of acute hepatitis and hepatomegaly are ruled out.⁹ The diagnosis should prompt exploration of barriers to poor glucose control, improved diabetes education, and close monitoring of glucose indices and diabetic complications.

Competing Interests: none declared.

References

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