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CASE REPORT | LIVER

Glycogenic Hepatopathy

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ABSTRACT

Glycogenic hepatopathy is excessive intrahepatic glycogen accumulation. It is a rare complication of long-standing, poorly controlled type 1 diabetes mellitus. We report a case of a 19-year-old woman with a history of poorly controlled diabetes mellitus and frequent admissions for diabetic ketoacidosis, who presented with abdominal pain, nausea, vomiting, and hepatomegaly. She was found to have diabetic ketoacidosis with persistently elevated serum lactate that did not improve with insulin infusions. She eventually underwent a liver biopsy, which showed excessive intracytoplasmic glycogen accumulation consistent with glycogenic hepatopathy.

INTRODUCTION

Glycogenic hepatopathy (GH) is excessive intrahepatic glycogen accumulation that manifests as hepatomegaly with transient elevation in serum aminotransferase enzymes. It is a rare complication of long-standing, poorly controlled type 1 diabetes mellitus (DM) and less commonly type 2 DM.[1] It was first reported by Mauriac in 1930 in children with type 1 DM as part of the Mauriac syndrome that includes hepatomegaly, growth retardation, cushingoid features, and obesity; however, it was later described in adolescents and young adults without the other components of the syndrome.[1-3] GH is rare and considered to be extremely underdiagnosed as it is difficult to be differentiated from nonalcoholic fatty liver disease (NAFLD), because it presents similarly and is seen with DM as well. The only way to make a definitive diagnosis and differentiate it from NAFLD is by liver biopsy, which is important as GH could be completely reversed with good glycemic control.[4]

CASE REPORT

A 19-year-old woman with a history of poorly controlled type 1 DM due to noncompliance and frequent admissions for diabetic ketoacidosis (DKA) presented with abdominal pain, nausea, and vomiting. Physical examination was significant for tender hepatomegaly. Laboratory workup was significant for serum glucose 185 mg/dL, bicarbonate 9 mmol/L, anion gap 38 mmol/L, beta-hydroxybutyrate 5.2 mmol/L, lactic acid 3.3 mmol/L, and glycated hemoglobin (HbA1c) 12.1%. Liver function was significant for alanine aminotransferase 29 U/L, aspartate aminotransferase 53 U/L, alkaline phosphatase 166 U/L, with normal bilirubin and prothrombin time. She was treated with insulin infusions and intravenous fluids for DKA, and her symptoms improved; however, her anion gap continued to be elevated despite normal beta-hydroxybutyrate. Her lactic acid was rechecked and came back at 8.8 mmol/L.

Abdominal computed tomography showed hepatomegaly with liver size of 20 cm in craniocaudal dimension. Workups for hepatitis A, B, C viruses, human immunodeficiency virus (HIV), autoimmune hepatitis, hemochromatosis, Wilson's disease, and celiac disease were negative. She underwent a liver biopsy that showed diffuse swelling of the hepatocytes and marked increase in intracytoplasmic glycogen consistent with GH (Figure 1). She was counseled on diabetic diet and proper insulin use to achieve strict glycemic control and was discharged home with a close follow-up.

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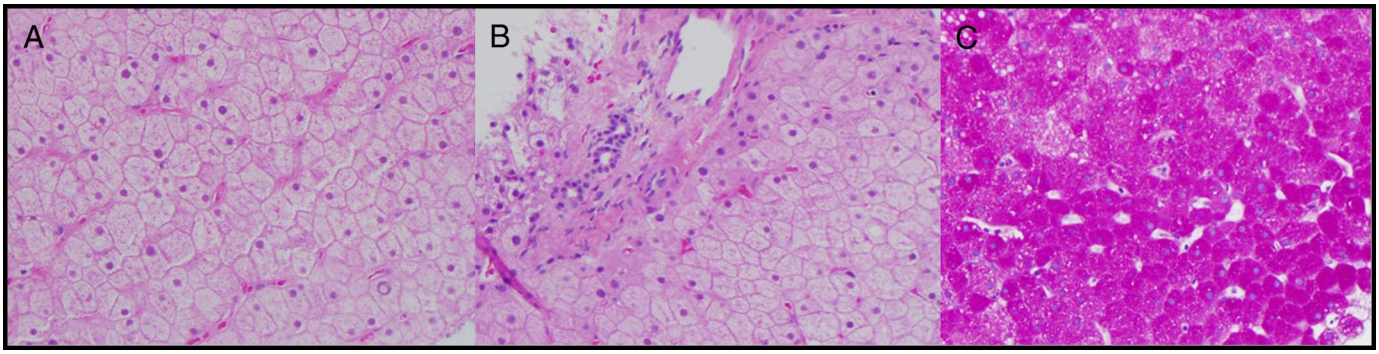

Figure 1. (A) Hematoxylin and eosin (H&E) stain of needle core liver biopsy showing pale, swollen hepatocytes without significant inflammation. Glycated nucleus is seen at the bottom right (20×). (B) The portal tracts appear normal with no inflammatory infiltrates, imparting a preserved hepatic architecture on H&E stain (40×). (C) Periodic acid-Schiff stain highlighting the glycogen content within the hepatocytes (20×).

DISCUSSION

The incidence of GH is unknown; however, it is believed to be underestimated. It is most commonly seen with type 1 DM but has also been reported with type 2 DM, short-term, high-dose steroid administration in children, and in dumping syndrome after Nissen fundoplication.[5–7] The exact mechanism behind it is not completely understood; however, fluctuations in the plasma levels of glucose in poorly controlled DM and the subsequent supraphysiologic doses of insulin administered to manage it are believed to be involved. It is unclear why some patients have the potential to develop it, and further research is needed to investigate this phenomenon.

GH is often seen in patients who present with frequent episodes of DKA as these patients are usually hyperglycemic and are treated with high doses of insulin. Their presentation ranges from asymptomatic elevation in liver enzymes to abdominal symptoms including abdominal pain, nausea, and vomiting.[8] The most common finding seen on physical examination is hepatomegaly which could be tender.[8] Ascites is less commonly seen but has been reported and is believed to be secondary to sinusoidal compression by the swollen, glycogen-laden hepatocytes.[4] Laboratory workup shows deranged liver enzymes, with mild to moderate elevations in liver aminotransferases (alanine aminotransferase and aspartate aminotransferase); however, marked elevations have been reported.[9] Alkaline phosphatase can be elevated, but it is less common and the liver synthetic function is usually normal.[10] HbA1c is frequently elevated, reflecting poor long-term glycemic control. Persistently elevated lactic acid can be seen in patients with GH who present with DKA without hypoperfusion.[11] The mechanism behind it is unclear. One theory is liver injury from glycogen accumulation can inhibit gluconeogenesis, therefore inhibiting the conversion of pyruvate to glucose and shifting its metabolism to lactate.[11] The administration of insulin would further inhibit gluconeogenesis and increase the lactate levels. A hypermetabolic state with accelerated glycolysis in the splanchnic region could be another contributing factor as it has been described in patients with acute and chronic liver disease causing elevated lactate levels.[12,13]

The diagnosis of GH requires ruling out other etiologies of liver injury that presents with elevated liver enzymes including viral hepatitis, autoimmune hepatitis, metabolic causes (hemochromatosis, Wilson's disease, and alpha-1 anti-trypsin deficiency), and drugs.[14] Glycogen storage diseases are genetic diseases that can result in glycogen accumulation in the liver due to deficiency in enzymes that regulate glycogen metabolism. GH and glycogen storage disease can present similarly, and differentiating between them by genetic testing is important given the wide differences in their management.[15]

NAFLD is another disease that can mimic GH in presentation and appearance on imaging, and ruling it out is crucial. A number of imaging modalities can be used to help in the diagnosis. Ultrasonography of the liver usually shows hepatomegaly; however, it is nonspecific and does not differentiate GH from NAFLD. Sweetser and Kraichely reported that computed tomography can help in differentiating the 2 conditions based on the differences in their appearance: GH having a bright hyperdense liver compared with a hypodense liver in NAFLD; however, it only provides qualitative information.[16] Gradient dual-echo magnetic resonance imaging has been reported to be effective in differentiating GH from NAFLD, with magnetic resonance spectroscopy being able to provide quantitative information, yet they are limited by their availability.[17,18]

Liver biopsy remains the gold standard in diagnosing GH and differentiating it from NAFLD. Hematoxylin and eosin stain generally shows pale, swollen hepatocytes filled with glycogen, associated with glycated nuclei and thickened plasma membranes (Figure 1). There is also preservation of the hepatocyte architecture, with no or minimal inflammation (Figure 1). Periodic acid-Schiff stain will be positive as it stains glycogen, and the addition of diastase will break down glycogen (Figure 1). Typically, hepatocytes will have no or minimal portal inflammation, steatosis, or fibrosis; however, there are recent reports of variable degrees of fibrosis including bridging fibrosis.[8] The implications of this has not been studied, and further research is needed to investigate its potential to progress to cirrhosis.

The mainstay of treatment is improving glycemic control, which usually results in improvement both clinically and biochemically in 2–14 weeks in most of the cases.[19] Recurrence of GH has been reported with repeated episodes of DKA; therefore, maintaining strict glycemic control is important.[20] Pancreatic transplantation has also been successful in reversing the disease with control of glucose metabolism afterward.[21]

DISCLOSURES

Author contributions: B. Sharma reviewed the literature and wrote the manuscript. M. Antoine and M. Shah wrote the manuscript. R. Nagales Nagamos provided the images. S. John edited the manuscript and is the article guarantor.

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