

# An Unusual Presentation of Glycogenic Hepatopathy with Bridging Fibrosis

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## ABSTRACT

Glycogenic hepatopathy is a rare and under-recognized complication of poorly controlled diabetes mellitus. We report a patient who presented with predominant elevation in alkaline phosphatase and liver biopsy showing bridging fibrosis, which is an unusual presentation of glycogenic hepatopathy. This case emphasizes the fact that glycogenic hepatopathy can also present with a cholestatic pattern of liver abnormality and with liver fibrosis, which warrants further study because severe fibrosis can progress to cirrhosis.

## INTRODUCTION

Glycogenic hepatopathy (GH) is a rare and under-recognized complication of diabetes mellitus that develops due to excessive accumulation of glycogen in the hepatocytes. GH occurs predominantly in patients with type 1 diabetes mellitus, and it occurs rarely in patients with type 2 diabetes mellitus.<sup>1-5</sup> GH was initially described as Mauriac syndrome by Pierre Mauriac in 1930 in children with poorly controlled type 1 diabetes mellitus due to its classic cushingoid features, hepatomegaly, and growth retardation.<sup>4,6</sup> Since then, multiple cases of GH have been reported, including in adolescents and young adults without the typical features, and this is now known as glycogenic hepatopathy.<sup>4</sup>

## CASE REPORT

A 44-year-old man with a known history of opioid abuse on a methadone program and a longstanding history of uncontrolled type 1 diabetes mellitus presented with abdominal pain with hyperglycemia and ketoacidosis. He denied alcohol use and was not on any regular medications except insulin. Physical examination revealed tender hepatomegaly. Abdominal sonography confirmed hepatomegaly, showing an enlarged liver that was 23.4 cm in length. Laboratory analysis was remarkable for markedly increased alkaline phosphatase (ALP) 1,003 U/L, aspartate aminotransferase 200 U/L, alanine aminotransferase 164 U/L, and gamma-glutamyl transpeptidase 1,224 U/L. Total bilirubin and coagulation tests remained normal.

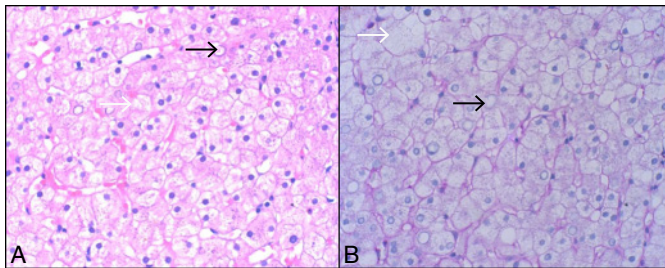
Upon presentation, the patient's serum glucose was 833 mg/dL and hemoglobin A1C was 11.1%. Workup for infectious hepatitis was negative. Serologies for antinuclear, anti-smooth muscle, and anti-mitochondrial antibodies as well as immunoglobulin level, iron studies, ceruloplasmin level, and angiotensin-converting enzyme levels were likewise negative. An echocardiogram revealed normal ejection fraction and no valvular heart disease. Subsequent magnetic resonance cholangiopancreatography showed no evidence of biliary obstruction. A week later, a liver biopsy showed enlarged hepatocytes with pale cytoplasm due to excess glycogen deposition and glycogenated nuclei, a finding consistent with GH. Increased hepatocyte glycogen was confirmed on a periodic acid-Schiff stain, and hepatocytes became "ghost cells" upon diastase digestion of the glycogen

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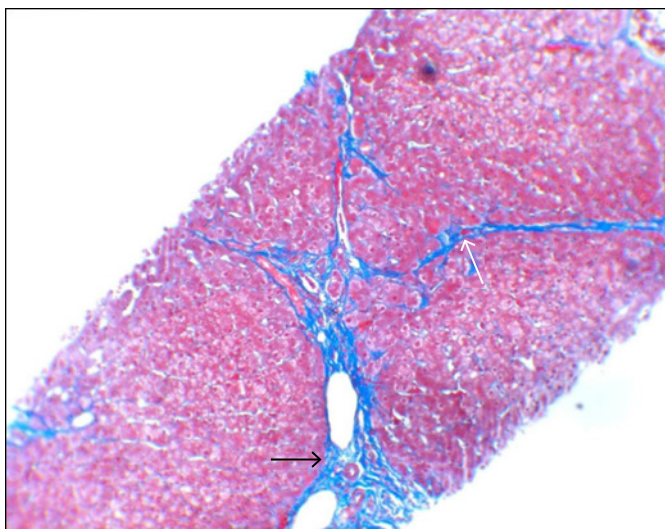


**Figure 1.** (A) Percutaneous liver biopsy with hematoxylin and eosin stain showing enlarged hepatocytes with cytoplasmic pallor, pink globules consistent with glycogen accumulation (white arrow), and prominent glycogenated nuclei (black arrow). (B) Diastase-periodic acid-Schiff stain with removed glycogen leaving empty-looking cytoplasm (white arrow) and nuclei (black arrow).

(Figure 1). Mild lobular inflammation with periportal and bridging fibrosis (F3 fibrosis) was also noted, which was an unusual finding for GH (Figure 2). Possible alternative contributors for fibrosis or marked ALP elevation were all excluded. Iron stains showed no hemosiderin, nor was there any significant steatosis. The patient’s hyperglycemia was managed with an aggressive insulin regimen, resulting in an improvement in his liver enzymes. Four weeks later, his liver enzymes, including ALP, were near normal. The patient was noncompliant with his medication and was subsequently re-admitted on several occasions with relapsing hepatitis and transient elevation in enzymes paralleling his elevated glucose level. These symptoms consistently returned to normal ranges with the control of his hyperglycemia.

**DISCUSSION**

The first description of GH coincides with the introduction of short-acting insulin for the treatment of diabetes, and its



**Figure 2.** Trichrome stain demonstrating multifocal periportal scarring (black arrow) with periportal bridging fibrosis (white arrow).

incidence decreased significantly with the introduction of longer-acting insulin and better control of diabetes. It is clinically challenging to distinguish GH from other causes of hepatomegaly associated with diabetes mellitus, such as nonalcoholic fatty liver disease (NAFLD) or hepatosclerosis.

The pathophysiology of GH is poorly understood, and it is unclear why only a fraction of patients with diabetes develop this entity. One of the essential elements identified for the development of GH was the wide fluctuation in the glucose and insulin levels.<sup>2,7</sup> The rapid action of soluble insulin along with administration of extra glucose to counteract the consequent hypoglycemia was thought to be the main driving force for the excessive accumulation of glycogen in the liver.<sup>8</sup> High serum glucose levels cause an influx of glucose into the hepatocytes, where they are rapidly phosphorylated. Subsequent treatment of high glucose with insulin causes further polymerization of trapped glucose into glycogen.

The presentation of GH can vary from an asymptomatic elevation in liver enzymes with hepatomegaly to symptoms associated with ketoacidosis, abdominal pain, nausea, or vomiting. Predominant elevation in aspartate aminotransferase and alanine aminotransferase were reported in most cases, whereas elevation in ALP with or without an increase in bilirubin is rare.<sup>2,8-10</sup> Liver synthetic functions are usually preserved. These enzyme elevations are considered to be caused by leakage of enzymes from hepatocyte cell death. GH presenting as a predominant elevation in ALP is unusual and has been rarely reported.<sup>2</sup> The increase in ALP is explained by the excessive glycogen deposition, with swollen hepatocytes eventually causing sinusoidal compression and cholestasis.<sup>11</sup>

GH is a distinct entity seen in diabetic patients that should be differentiated from the more common NAFLD pathology. Liver ultrasound or computed tomography (CT) of the abdomen may not be a useful modality, although a bright liver on CT imaging can be a clue in favor of GH.<sup>10</sup> Gradient dual-echo magnetic resonance imaging (MRI) was reported to distinguish fat deposition in NAFLD from GH. T1-weighted gradient-dual-echo MRI images with in-phase and opposed-phase conditions could effectively differentiate hepatic glycogen from the fat seen in NAFLD.<sup>12</sup> Fat contents are obtained from images in which the signal intensity at in-phase is higher than that at opposed-phase. If there is no significant difference in the signal intensities between the two images, they are not consistent with intrahepatic fat storage.<sup>12</sup>

A definitive diagnosis of GH can be made only with liver biopsy. Biopsy in our case also showed F3 bridging fibrosis, which had been reported in only two cases in the literature.<sup>13</sup> The exact mechanism leading to the development of fibrosis in GH is unclear. Diabetic hepatosclerosis is a form of diabetic microangiopathy affecting the liver that can produce significant fibrosis.<sup>14</sup> However, fibrosis in hepatosclerosis is usually

perisinusoidal and is unlikely to be the cause of fibrosis in our case.

Despite showing regression of hepatomegaly and normalization of liver enzymes with strict glycemic control, GH could recur when blood sugar is not properly maintained.<sup>15</sup> It is important to recognize that GH can present with predominant cholestasis and can produce liver fibrosis. Bridging fibrosis in GH merits further studies, as this could progress to cirrhosis.

## DISCLOSURES

Author contributions: All authors contributed equally to the manuscript. JM Sherigar is the article guarantor.

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Informed consent was obtained for this case report.

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