

Diagnosing glycogen storage disease type 1b in adulthood: A case with multiple hepatocellular adenomas

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Abstract

Glycogen Storage Disease Type 1b (GSD Type 1b) is predominantly diagnosed in childhood. Rare cases emerging in adulthood present a unique set of clinical challenges, particularly concerning liver lesions. We report a 22-year-old male diagnosed unusually late with GSD Type 1b, underlining the hepatic complexities involved. He initially presented with hepatomegaly and solid nodular lesions in the liver. An abdominal magnetic resonance imaging (MRI) revealed a sizable hepatocellular adenoma (HCA), subsequently removed through surgical segmentectomy. Histopathology confirmed the lesion as a hepatocyte nuclear factor-1 alpha (HNF-1alpha) mutation-positive HCA. Follow-up MRI revealed the persistence of multiple smaller liver nodules, necessitating continued clinical surveillance. Hepatic adenomas are a common complication in GSD Type 1 patients, posing management challenges due to their size, multiplicity, and risk of malignancy. While liver transplantation is a last resort option, it can worsen metabolic control. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors offer a potential alternative for improving glycemic regulation and possibly affecting the adenoma size.

Keywords: Hepatic adenoma; hepatology; glycogen storage disease; SGLT-2.

Introduction

Hereditary deficiencies in enzymes involved in glycogen metabolism lead to glycogen storage diseases (GSD). In GSD Type 1, the metabolism of glucose-6-phosphate, located in the pentose phosphate pathway, is disrupted. A deficiency in Glucose-6-phosphate dehydrogenase (G-6PD) leads to GSD Type 1a, while a deficiency in the Glucose-6-phosphate transporter (G6PT)—which transports G6P from the cytoplasm to the endoplasmic reticulum lumen—leads to GSD Type 1b. Individuals with Type 1 GSD may develop hypoglycemia and lactic acidosis during the neonatal period; however, more commonly, they exhibit hepatomegaly at 3–4 months of age.^[1] Although GSD Type 1 is usually diagnosed in child-

hood, it is very rarely diagnosed in adulthood.^[2–4] Hepatocellular adenoma (HCA), hepatocellular carcinoma (HCC), hepatoblastoma, focal fatty infiltration, focal fatty sparing, focal nodular hyperplasia, and peliosis hepatis are some of the liver lesions noted in GSD Type 1 patients.^[5] Historically, 70–80% of patients older than 25 years have at least one lesion.^[5]

We report an intriguing case of a patient with GSD Type 1b who was diagnosed at the age of 22 and is still under follow-up for his hepatocellular adenomas (HCA). The case underscores the complexity of managing hepatic adenomas due to their size, multiplicity, and potential for malignancy. It also highlights the emerging role of SGLT-2 inhibitors as a promising therapeutic approach in glycogen storage diseases, particularly in managing liver adenomatosis, a critical aspect requiring further research for confirmation.

Case Report

Patient History

The patient's medical history revealed growth retardation and fatigue at 7 years of age, resulting in hospital admission. Despite consanguinity between his parents, there was no known history of metabolic disease in the family. His condition remained undiagnosed, and he was subsequently monitored. At 13 years of age, he presented to our clinic with growth retardation and hypertriglyceridemia. The patient's follow-up period was irregular between 13 and 22 years of age. Following evaluation by the endocrinology, pediatric metabolism, and genetics departments, he was diagnosed with GSD Type 1b at 22 years of age. His medication history was limited to fenofibrate and he had no history of alcohol consumption. Abdominal ultrasonography revealed a solid nodular lesion with heterogeneous internal structures in the liver during the follow-up.

The medical evaluation documented a patient's stature of 150 cm and mass of 43 kg, resulting in a BMI of 19.1. An enlarged liver was noted during the abdominal assessment, with no other abnormal findings. Blood tests indicated slightly increased liver enzyme levels and elevated triglyceride levels (ALT, 54 U/L; GGT, 75 U/L; and triglycerides, 473 mg/dL). The patient's viral hepatitis markers were negative, except for a positive anti-HBs result, and the AFP was 1.2 ng/mL. In addition to these findings, no other irregularities were detected in the blood. The patient had no prior medical condition or history of alcohol consumption.

Abdominal magnetic resonance imaging (MRI) was performed upon referral to our clinic. MRI findings showed a single 6x4.5 cm lesion in the liver, located in segments 2–3, which had clear margins and were attenuating to the liver. Following the contrast administration, the lesion exhibited transient, homogeneous enhancement that dissipated upon portal venous and delayed phase images, returning to near isodensity.

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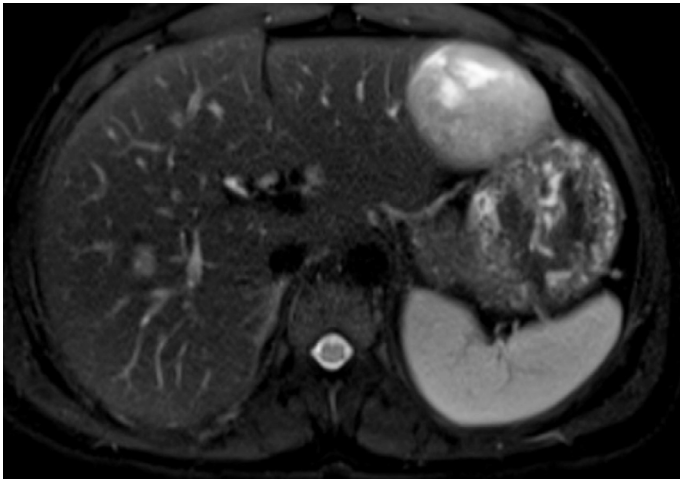


Figure 1. Single 6x4.5 cm lesion in the liver.

There was no rapid washout, infiltrative appearance, marked diffusion restriction, or rim enhancement, by HCC or metastatic lesions. Although the lesion demonstrated clear margins and was attenuating to the liver, its lack of a central scar as a hypodense lesion did not align with the characteristics of focal nodular hyperplasia. There was no cirrhotic appearance of the liver or any sign of portal hypertension. (Fig. 1)

The necessity for surgical excision of the lesion was indicated by the radiological features suggestive of HCA as well as the size of the lesion, which exceeded 5 cm, and the diagnosis of GSD, which predisposes such patients to develop HCA. Consequently, we referred the patient to the general surgery department, where a segmentectomy was performed. There was no deterioration in liver function after surgical excision. Pathological findings were positive for beta-catenin, membranous portal vein embolism (PVE), and glutamine synthetase, and the lesion was reported as an HNF-1alpha mutation-positive hepatocellular adenoma (Fig. 2). We continued to follow-up the patient for almost 4 years after surgery, and his last liver function test and clinical condition were normal; however, his recent abdominal MRI 6 months prior revealed multiple nodular lesions in his liver, the largest of which measured 1.5x1 cm. A reevaluation of the patient was conducted following the recurrence of liver HCA's. The initiation of sodium-glucose cotransporter 2 (SGLT-2) was withheld due to insufficient data in the literature.

Discussion

Although GSD Type 1 is typically diagnosed in childhood, some cases are diagnosed in adulthood, often presenting with hepatocellular adenomas.^[2-4] Among the liver lesions observed in GSD Type 1 patients—such as hepatocellular adenoma (HCA), hepatocellular carcinoma (HCC), hepatoblastoma, focal fatty infiltration, focal fatty sparing, focal nodular hyperplasia, and peliosis hepatis—HCAs are the most common.^[5] These generally appear in the second or third decade of life, with reported frequencies ranging from 16% to 75%.^[6,7] Historically, 70–80% of patients older than 25 years have had at least one lesion.^[5] Despite the presence of hepatomegaly, liver enzyme levels are usually normal or near normal.^[1] An elevation in liver enzymes may occasionally be noted early in the disease course, typically around the time of diagnosis.^[5] Abdominal imaging can be utilized to investigate liver enzyme elevation, and the identification of multiple liver lesions may lead to a diagnosis of GSD. After detection, 50% of cases exhibit progression in the size and/or number of adenomas during follow-up.^[8]

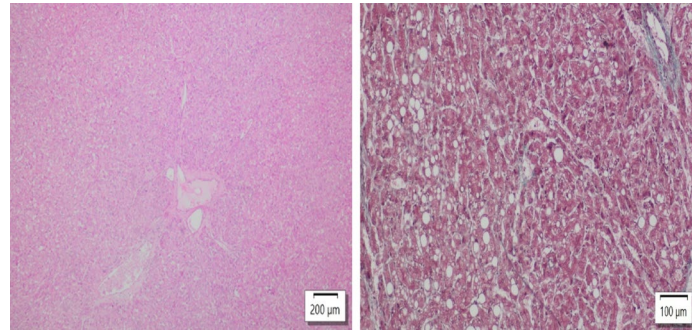


Figure 2. The lesion can be formed as a result of mature hepatocyte proliferation in the form of well-circumscribed, 1–2 cell thick cell layers. Cytological atypia is not observed. Interlobular bile ducts accompanying the hepatic artery are not observed in the portal area.

Such adenomas are more likely to have a lobular distribution than those in the general population.^[5]

Patients diagnosed with GSD Type 1 are now living longer than before, leading to the recognition of new long-term complications. HCC is one such complication. The cause of HCC remains unclear, but there appears to be a transformation from adenoma to HCC, rather than HCC arising in normal liver tissue.^[5]

Inadequate metabolic regulation may also be a contributing factor in the onset of hepatocellular adenomas (HCA) in individuals with Glycogen Storage Disease Type 1 (GSD Type 1) and existing research supports the notion that achieving optimal metabolic control can mitigate the risk of developing adenomas.^[9] However, it is important to note that even excellent metabolic regulation may not suffice to completely prevent the occurrence of HCA in some GSD Type 1 patients.^[5] Studies have shown that sodium-glucose co-transporter-2 (SGLT-2) inhibitors can enhance metabolic stability by lowering plasma 1.5-anhydroglucitol levels, positioning them as a viable therapeutic strategy for conditions such as neutropenia and neutrophil dysfunction.^[10] One significant drawback of using SGLT-2 inhibitors in GSD Type 1 patients is the increased risk of hypoglycemia.^[10] Given these considerations, we suggest that SGLT-2 inhibitors may also serve to decrease the incidence of adenomas through improved metabolic control, thereby offering a prospective treatment option for GSD Type 1 patients with HCA. Prospective well-designed studies are needed to confirm the efficacy of SGLT-2 inhibitors in the management of HCA's. The management of these lesions remains unclear. Liver imaging is routinely performed in individuals with GSD Type 1. Laboratory tests, conducted every six months to a year, should include serum transaminases, creatinine, international normalized ratio (prothrombin time/partial thromboplastin time), albumin, and bilirubin to monitor the extent of hepatic damage and assess the progression of liver disease, especially in the context of liver transplantation (LT).^[5] It is also established that α -fetoprotein and carcinoembryonic antigen levels do not predict the presence of HCAs or malignant transformation in GSD Type 1 patients.^[7,11] A conservative approach is recommended for treating hepatocellular adenomas in GSD Type 1.

Hepatocellular carcinoma (HCC) is an indication for liver transplantation (LT) in patients with GSD Type 1. However, due to the potential for worsened metabolic control with immunosuppressive therapy and declining renal function, LT is generally not recommended for GSD Type 1 patients.^[12-15]

Our patient underwent HCA resection due to the lesion's significant size and malignant potential. He continues to be followed up for his adenomas.

Conclusion

Hepatic adenomas frequently manifest as a complication in patients with GSD Type 1. Therefore, it is crucial to monitor such patients for the development of HCA. The considerable dimensions of these adenomas, their propensity to occur in multiple numbers, and the associated risk of malignancy collectively render their management a complex endeavor. LT serves as a last resort but may exacerbate already suboptimal metabolic control. SGLT-2 inhibitors are used as novel treatments for glycogen storage diseases and could be a potential therapy also for the management of liver adenomatosis in GSD disorders. In summary, managing HCA is a challenging task, both in terms of diagnosis and management. To effectively address these cases, it is vital to implement a proven management approach.

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