

Case Report

Glucocorticoid-induced rapid development of glycogenic hepatopathy in a liver transplant patient with no prior history of diabetes mellitus: a case report

Vanda F Torous¹, Abtin Farahmand², Sergei Tatishchev³, Hanlin L Wang⁴

¹Department of Pathology and Laboratory Medicine, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, USA; ²Department of Internal Medicine, David Geffen School of Medicine, University of California, Los Angeles, 10833 Le Conte Avenue, Los Angeles, CA 90095, USA; ³Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California Los Angeles, 10833 Le Conte Avenue, Los Angeles, CA 90095, USA; ⁴Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California Los Angeles, 10833 Le Conte Avenue, Los Angeles, CA 90095, USA

Received June 16, 2016; Accepted June 23, 2016; Epub August 20, 2016; Published August 30, 2016

Abstract: Glycogenic hepatopathy is a distinct clinicopathologic entity in which there is a pathologic overloading of hepatocytes with glycogen. Classically, it has been described in association with poorly controlled diabetes mellitus types I and II in both pediatric and adult populations. While the majority of the few studied cases on this disease entity describe cases in which glycogenic hepatopathy presents in diabetic patients with hepatomegaly, abdominal pain, and elevated transaminases, there is a wider differential that should be considered, including medication effect, particularly with short-term, high-dose steroid use. We herein report the first case of glycogenic hepatopathy developing in a non-diabetic adult patient following immunosuppressive steroid therapy in the setting of liver transplantation. This case illustrates that glycogenic hepatopathy can develop rapidly in patients with glucocorticoid-induced hyperglycemia. Glycogenic hepatopathy should be included in the diagnostic work-up of posttransplant patients with abnormal liver function tests and poor glycemic control.

Keywords: Glycogenic hepatopathy, transplant, steroid, diabetes mellitus

Introduction

Elevation of the serum liver enzyme levels in the early post-liver transplant period can be secondary to a variety of conditions, such as ischemic injury, rejection, biliary obstruction, and infections. Glycogenic hepatopathy (GH) is an under-recognized cause of transaminitis and is rarely considered in the setting of liver transplantation, especially in patients with no prior history of diabetes mellitus. It occurs when there is a disruption in the balance between glycogenesis and glycogenolysis that leads to an excessive accumulation of glycogens in the hepatocytes. It has been described as a disease that causes hepatomegaly and liver injury with elevations of serum transaminases. The published literature primarily concerns cases that arise in the background of uncontrolled diabetes mellitus in non-transplant adult and pediatric patients. It is impor-

tant to note, however, that GH can occur whenever there is a disruption of the glycogen metabolism pathway for a variety of reasons, and not just in patients with diabetes.

We herein describe an interesting case of a patient who had no prior history of diabetes mellitus and who underwent liver transplantation for cirrhosis secondary to alcohol abuse and hemochromatosis. During the post-transplant course, the patient's blood glucose levels were increasingly difficult to control after the administration of high dose steroid therapy. A liver biopsy revealed features consistent with GH. This unique case presentation demonstrates the importance of recognizing this entity in not just diabetic patients, but also those receiving medications that can alter the glucose metabolic pathway such as steroid therapy in the post-transplant patient population.

Glucocorticoid-induced glycogenic hepatopathy

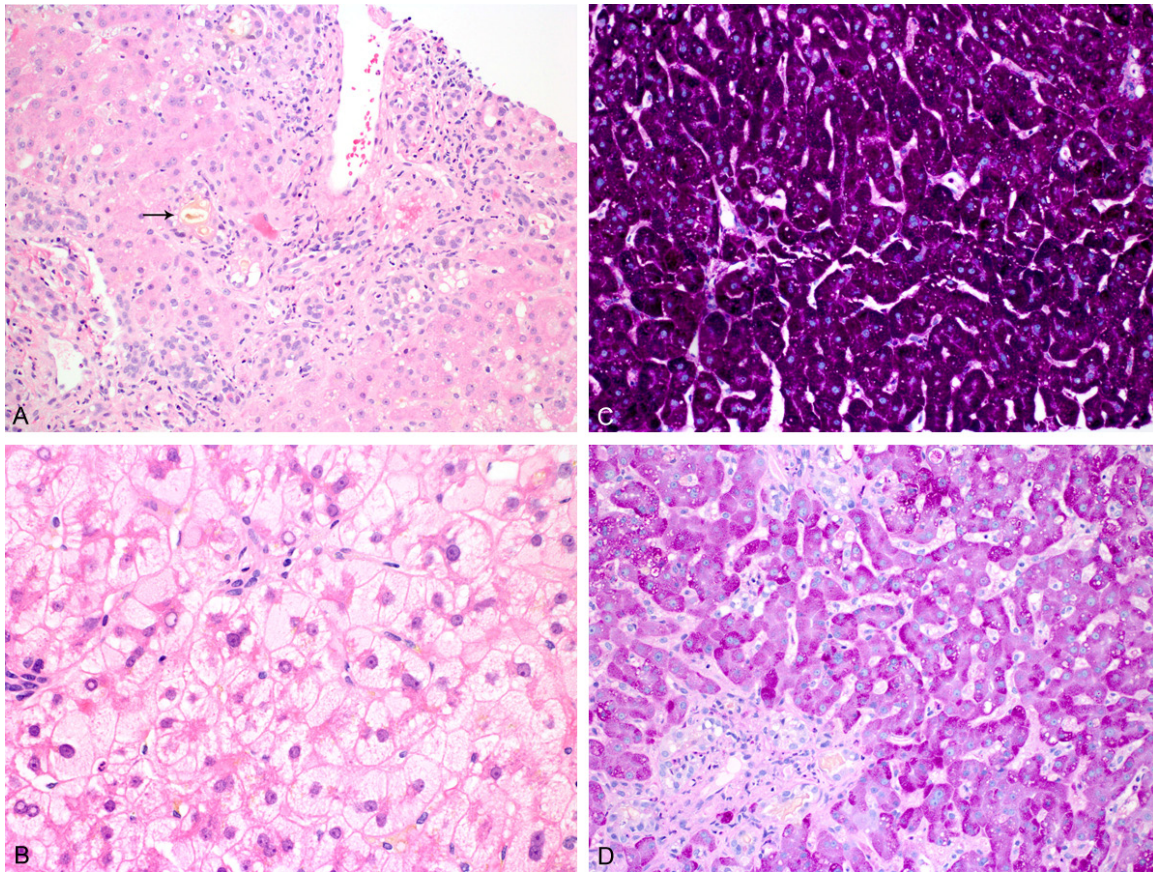


Figure 1. A. Cholangitis lenta demonstrated in the allograft biopsy performed two weeks post transplantation. Note the presence of inspissated bile in dilated ductules (arrow). There are mild portal inflammatory cell infiltrates rich in neutrophils. There is no significant portal edema. No endotheliitis is observed (hematoxylin and eosin stain, original magnification x200). B. Striking glycogen accumulation in hepatocytes demonstrated in the allograft biopsy performed five weeks post transplantation. Note that the hepatocytes exhibit pale and expanded cytoplasm, consistent with glycogen accumulation (hematoxylin and eosin stain, original magnification x400). C. Glycogen accumulation noted in the biopsy performed five weeks post transplantation was confirmed by strong periodic acid-Schiff stain (original magnification x200), which was sensitive for diastase digestion. D. For comparison, glycogen accumulation was much less prominent in the biopsy performed two weeks post transplantation (periodic acid-Schiff stain, original magnification x200).

Case report

The patient is a 42-year-old female who underwent orthotopic liver transplantation for decompensated cirrhosis due to alcohol abuse and hemochromatosis. The post-transplant course was complicated by sepsis, coagulopathy, pulmonary embolization, and acute renal failure.

Following an acute elevation of serum transaminase and bilirubin levels two weeks after the transplantation, the patient underwent a needle biopsy of the liver. Histologic examination showed features of cholangitis lenta (also known as subacute nonsuppurative cholangitis) characterized primarily by ductular reaction

with inspissated bile in dilated ductules (**Figure 1A**). These findings were not observed in the post-perfusion tru-cut biopsy performed during transplantation surgery, which showed only mild preservation injury and minimal steatosis. The findings of cholangitis lenta were believed to be compatible with the clinical history of post-transplant sepsis. No features of acute cellular rejection, biliary obstruction, or infectious agents were demonstrated in this biopsy.

Three weeks after the initial biopsy (five weeks post transplantation) another liver biopsy was performed due to continued elevation of liver enzymes despite clinical improvement of patient's overall conditions. In addition to

Glucocorticoid-induced glycogenic hepatopathy

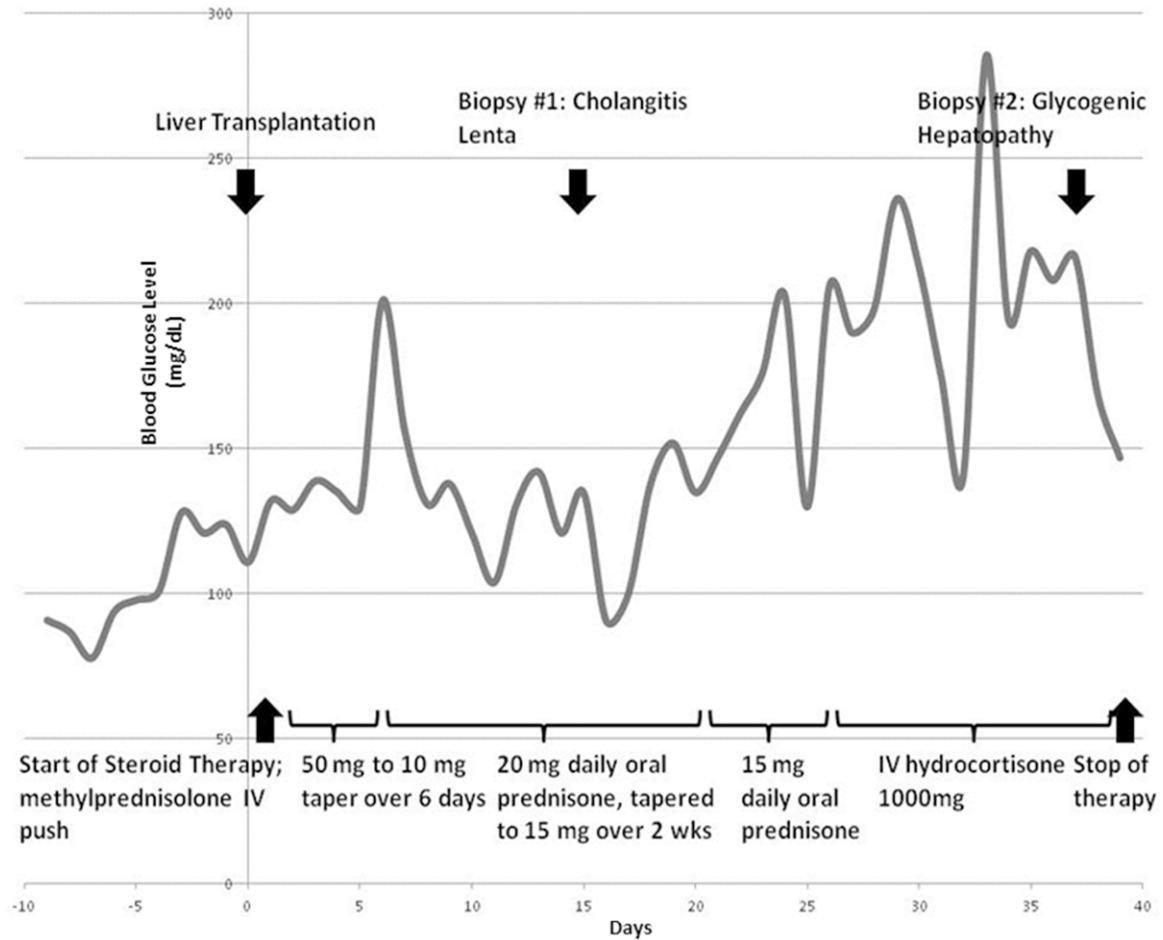


Figure 2. Blood glucose levels in relation to time course of steroid therapy. Note that the normal range of blood glucose is 65-99 mg/dL.

resolving features of cholangitis lenta, a striking degree of glycogen accumulation within hepatocytes was observed in this biopsy (**Figure 1B** and **1C**). Again, no features of acute cellular rejection, biliary obstruction or infectious agents were demonstrated. On retrospective review, glycogen accumulation was not prominent in the prior liver biopsy performed three weeks prior (**Figure 1D**) or in the post-perfusion tru-cut biopsy.

Given the liver biopsy findings, which were compatible with a diagnosis of GH, review of her laboratory results was performed. She was found to have persistently elevated blood glucose levels post transplantation, which paralleled steroid therapy (**Figure 2**). It was clinically noted that the patient's glucose levels became progressively problematic to manage while post-transplant steroid therapy continued. The patient did not have a history of diabetes mel-

litus and had been evaluated for diabetes prior to liver transplantation. Her most recent tests prior to transplantation revealed a glucose level of 106 mg/dL (normal range: 65-99) and a hemoglobin A1c level of 3.4%.

Following three months of hospital stay, the patient's overall status improved and she was discharged to a skilled nursing facility. However, two weeks later the patient was readmitted and subsequently expired in the setting of sepsis, acute respiratory distress syndrome, and disseminated intravascular coagulation.

Discussion

In 2006, Torbenson et al proposed a unifying term of "glycogenic hepatopathy" to describe characteristic histologic findings in the livers of patients with hepatomegaly and/or elevated transaminase levels in the setting of prolonged

Glucocorticoid-induced glycogenic hepatopathy

hyperglycemia [1]. GH was first recognized in 1930 by Mauriac as a part of the eponymous syndrome, and has been identified under a number of different terms since then, including “hepatic glycogenosis”, “liver glycogenosis”, “liver glycogen storage”, and “diabetes mellitus-associated glycogen storage hepatomegaly” [2-5]. Typically, GH is found in association with poorly controlled type I diabetes mellitus. Hepatomegaly is the most characteristic clinical manifestation. In addition to transaminitis, which can fluctuate over time [6], other laboratory values include hyperglycemia, ketoacidosis, and hyperlipidemia [1, 6-10]. GH does not appear to affect the synthetic function of the liver, and thus is not associated with clotting abnormalities or hypoalbuminemia.

From a pathophysiologic standpoint, glucose passively enters hepatocytes in a process driven by a high glucose concentration gradient, and is then converted into glycogen within the cells. Over a period of time, when enough glycogen is trapped within the cytoplasm, the cells swell and display a distinct histomorphologic appearance. When a liver specimen is microscopically examined, the most prominent finding is the presence of pale-appearing, swollen hepatocytes with accentuation of the cell membranes and compressed sinusoidal spaces. PAS stain highlights abundant diastase-sensitive intracellular glycogen deposits. Glycogenated nuclei may also be seen. Steatosis may be present, but this has been found only in a minority of cases [1]. The overall histologic findings may appear similar to those found in glycogen storage diseases, but may be more subtle [11].

In our case, the development of GH appears to be the direct consequence of immunosuppressive steroid therapy following liver transplantation. Glucocorticoid-induced hyperglycemia in this patient resulted in a rapid accumulation of glycogens in hepatocytes within five weeks. The exact mechanism(s) that led to rapidly developing GH in this patient is unknown but might be unique to the enzymatic activity in the allograft liver. Based on a study by Iancu et al, which examined the effects of short-term high-dose steroid therapy in children with varying underlying medical conditions, it appears that only a subset of individuals develops hepatomegaly with histologically confirmed GH [12]. Two

recent case reports on patients with diabetes mellitus type I have also shown that GH can develop rapidly in the setting of poor glycemic control alone [13, 14]. In both patients, GH resolved following insulin treatment.

In conclusion, our case illustrates that medications (such as glucocorticoids) can lead to fairly rapid development of GH in non-diabetic post-transplant patients with poor glycemic control. It is important to recognize this unique clinicopathologic entity to avoid confusions with other post-transplant complications. Although we could not provide clinical and histologic follow-up data due to patient’s demise, the available literature suggests that GH can be rapidly reversed with improved glycemic control. This also makes the histologic recognition important.

Address correspondence to: Dr. Vanda F Torous, Department of Pathology and Laboratory Medicine, Harvard School of Medicine, 330 Brookline Avenue, Boston MA 02215, USA. Tel: 617-667-4233, Fax: 617-667-4533; E-mail: vtorous@bidmc.harvard.edu

References

- [1] Torbenson M, Chen YY, Brunt E, Cummings OW, Gottfried M, Jakate S, Liu YC, Yeh MM, Ferrell L. Glycogenic hepatopathy: an underrecognized hepatic complication of diabetes mellitus. *Am J Surg Pathol* 2006; 30: 508-513.
- [2] Mauriac P. Gros ventre, hepatomegalie, troubles de la croissance chez les enfants diabetiques traits depuis plusieurs annees par l’insuline. *Gaz Hebd Med Bordeaux* 1930; 26: 402-410.
- [3] Evans RW, Littler TR, Pemberton HS. Glycogen storage in the liver in diabetes mellitus. *J Clin Pathol* 1995; 8: 110-113.
- [4] Nakamuta M, Ohashi M, Goto K, Tanabe Y, Hiroshige K, Nawata H. Diabetes mellitus associated glycogen storage hepatomegaly: report of a case and review of the Japanese literature. *Fukuoka Igaku Zasshi* 1993; 84: 354-358.
- [5] Torres M, Lopez D. Liver glycogen storage associated with uncontrolled type 1 diabetes mellitus. *J Hepatol* 2001; 35: 538.
- [6] van de Brand M, Elving LD, Drenth JP, van Krieken JH. Glycogenic hepatopathy: a rare cause of elevated serum transaminases in diabetes mellitus. *Neth J Med* 2009; 67: 394-396.
- [7] Sweetser S, Kraichely RE. The bright liver of glycogenic hepatopathy. *Hepatology* 2010; 51: 711-712.

Glucocorticoid-induced glycogenic hepatopathy

- [8] Olsson R, Wesslau C, William-Olsson T, Zettergren L. Elevated aminotransferases and alkaline phosphatases in unstable diabetes mellitus without ketoacidosis or hypoglycemia. *J Clin Gastroenterol* 1989; 11: 541-545.
- [9] Manderson WG, McKiddie MT, Manners DJ, Stark JR. Liver glycogen accumulation in unstable diabetes. *Diabetes* 1968; 17: 13-16.
- [10] Bassett JT, Veerappan GR, Lee DH. Glycogenic hepatopathy: a rare cause of increased aminotransferase levels in a diabetic patient. *Clin Gastroenterol Hepatol* 2008; 6: A26.
- [11] Torbenson M. Glycogenic abnormalities on liver biopsy. In: Ferrell L, Kakar S (eds) *Consultant Pathology Series: Liver Pathology*. Demos Medical Publishing, LLC, New York, 2011. pp. 251-263.
- [12] Iancu TC, Shiloh H, Dembo L. Hepatomegaly following short-term high-dose steroid therapy. *J Pediatr Gastroenterol Nutr* 1986; 5: 41-46.
- [13] Saxena P, Turner I, McIndoe R. Glycogenic hepatopathy: a reversible condition. *J Gastroenterol Hepatol* 2010; 25: 646.
- [14] Saadi T. Glycogenic hepatopathy: a rare disease that can appear and resolve rapidly in parallel with glycemic control. *Isr Med Assoc J* 2012; 14: 269-270.