We read with great interest the paper by Asada et al. (1) regarding a patient with type 1 diabetes mellitus (T1DM) and glycogen hepatopathy (GH). For a long time, this case had been misdiagnosed as nonalcoholic fatty liver disease (NAFLD), which is more common in T2DM and which may - at least in part - lead to liver fibrosis. This case report suggests that when patients with T1DM liver abnormalities present with uncontrolled hyperglycemia, it is important to recognize the occurrence of GH and to distinguish this clinically from NAFLD. The term “GH”, which was first coined by Torbenson et al. (2), describes the pathologic overloading of hepatocytes with glycogen that is associated with poorly controlled T1DM. GH can lead to hepatic enlargement, modestly elevated transaminase levels, and sometimes abdominal pain, nausea, and vomiting.

GH cannot be distinguished from NAFLD by ultrasound (US) and a firm diagnosis ultimately requires a liver biopsy. Periodic Acid-Schiff (PAS) staining (as was performed in this case) before and after diastase digestion should be performed to differentiate GH from NAFLD. PAS with diastase (PAS-D) refers to the use of the PAS staining in combination with diastase which is an enzyme that digests the glycogen. The purpose of the PAS-D procedure is to differentiate glycogen from other PAS-positive elements in tissue samples (3). Enlarged pale hepatocytes with abundant cytoplasmic glycogen deposits are demonstrated by PAS staining, while and diastase digestion removes the glycogen, resulting in “ghost cells” (4). PAS-D has been believed to be essential for distinguishing between GH and other diseases.

In Japan, there are accumulating case reports on GH (5, 6). Ikarashi et al. reported four cases of GH with uncontrolled T1DM which were confirmed histologically (6). Since liver biopsy has several drawbacks (i.e., cost, sampling errors, risk and observer variability), several recent studies have explored non-invasive methods of diagnosing GH. The serum lactate and lactate to pyruvate ratios are elevated in T1DM patients with GH (7, 8). The normal lactate range is less than 1.3-2.3 mmol/L (9). Some reports investigated the serum lactate levels in patients with GH. Four young patients had serum lactate levels of 3.1-10.8 mmol/L (7). The median level (ranges) of serum lactate in 31 children with GH was 2.8 (1.2-9.0) mmol/L (8). However, this case had an almost normal lactate level (2.3 mmol/L). Whether the determination of the serum lactate level is useful for predicting GH remains to be determined. The most important problem is that the feature of elevated lactate levels in GH is not well-recognized by clinicians.

NAFLD results in a hypodense liver; in contrast, the liver of GH patients is hyperdense (4). According to a paper by Ikarashi et al. (6), a hyperdense liver was observed on CT scans of T1DM patients with GH. It has been suggested that GH can be identified by CT, since other causes of a marked increase in hepatic attenuation (75 Hounsfield units) on unenhanced CT are limited to conditions in which radiodense material (i.e., iodine) is deposited in the liver in hemochromatosis patients using amiodarone and iron overload (4). In this case, however, the CT density was diffusely decreased in the liver. It is suggested that the GH liver can be hypodense on CT due to co-existing acute liver injury. Two recent case reports from Japan demonstrated that gradient dual-echo magnetic resonance imaging (MRI) can effectively differentiate glycogen from hepatic fat (10, 11). T1-weighted gradient-dual-echo MRI is recorded with in-phase and opposed-phase conditions. In NAFLD patients, the signal intensity in the in-phase is greater than that in the opposed-phase. However, there is no significant difference in the signal intensities between the two images in GH patients. They subsequently recommended the addition of dual-echo MRI to the radiological evaluation.

Fitzpatrick et al. (8) reported the existence of fibrosis on liver biopsy in 73% of 19 subjects with GH. Although bridging fibrosis was observed in two specimens, the degree...
of fibrosis was generally mild. This case also had mild pericellular fibrosis. Consistent with these studies, four cases from Japan (6) showed mild (or no) fibrosis. There is still a need for larger-scale and long-term studies to explore the consequences of fibrosis over time. US elastography (Fibroscan) or magnetic resonance elastography (MRE) may play a role in evaluating the degree of fibrosis in patients with GH.

Improving glycemic control is known to be the mainstay of treatment for GH. It differs clinically from NAFLD in that the symptoms associated with GH typically resolve rapidly with the improvement of diabetes control; this improvement does not occur in patients with NAFLD (12). GH is a benign condition that can potentially be reversed (both clinically and biochemically) within 2 to 14 weeks with good glycemic control.

In summary, GH should be distinguished from NAFLD as a cause of hepatomegaly and liver functional abnormalities in T1DM. Although liver biopsy using PAS-D is now the gold standard for the final diagnosis of GH, non-invasive methods for the diagnosis of GH, including the measurement of the serum lactate levels and MRI, are expected to be established in the near future (13).

Author’s disclosure of potential Conflicts of Interest (COI).
Yosio Sumida: Honoraria, Mitsubishi Tanabe, Sumitomo Dainippon, Astrazeneca and MSD. Masashi Yoneda: Honoraria, Mitsubishi Tanabe, Sumitomo Dainippon, Astrazeneca, MSD and Bristol-Myers Squibb.

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