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CASE REPORT | LIVER

A Rare Case of Tirzepatide-Induced Hepatotoxicity

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ABSTRACT

Tirzepatide is the first dual incretin glucose-dependent insulinotropic polypeptide/glucagon-like peptide 1 receptor activator approved for the management of type II diabetes mellitus. This drug was also recently approved by the Food and Drug Administration as a management option for patients with obesity. Tirzepatide has been also reported to be beneficial in reducing liver fat content. Although its efficacy is well described in the literature, no cases of tirzepatide-induced hepatotoxicity have been reported. We report a case of a 37-year-old woman with metabolic syndrome who was noted to have elevated liver enzymes secondary to tirzepatide use.

KEYWORDS: tirzepatide; hepatotoxicity; liver injury

INTRODUCTION

There has been a rapid increase in the incidence and prevalence of diabetes mellitus (DM) and obesity in the last few decades. Recent studies have reported that the prevalence of DM doubled from 3.2% in 1990 to 6.5% in 2021, and that of obesity has increased from 4.6% in 1990 to 14% in 2019.[1,2] The treatment landscape for type II DM and obesity has significantly changed over the last 2 decades, with the introduction of incretin mimetics.[3] Recently, tirzepatide, a combined glucose-dependent insulinotropic polypeptide/glucagon-like peptide 1 (GLP-1) agonist, was approved as a treatment option for diabetes in May 2022.[4] This drug has been shown to improve glycemic control by stimulating insulin release from the pancreas and has been reported to be superior to GLP-1 agonists in improving hemoglobin A1C levels.[5] It has also been reported that tirzepatide injection once a week results in significant weight loss in obese patients.[6] Tirzepatide has also been shown to have beneficial effects on the liver, and its use has been associated with significant reduction in liver fat content.[7] However, as of this report, there have been no reports of liver-related adverse events. We present a rare case of tirzepatide-induced liver injury in a 37-year-old woman.

CASE REPORT

A 37-year-old woman with a medical history of obesity, hypertension, and hypercholesterolemia was referred to our clinic for elevated liver enzymes. The patient denied any symptoms such as nausea, vomiting, abdominal distension, jaundice, or episodes of confusion. Physical examination was normal. She denied any supplement use, excessive alcohol use, or family history of autoimmune disease. Her medications included ethinyl estradiol 0.15 mg/levonorgestrel 30 mg for birth control and tirzepatide. She was initiated on tirzepatide 2.5 months before presentation and was on birth control medication for more than 10 years. She also reported losing 30 pounds since starting tirzepatide. Her blood tests on presentation revealed an alanine transaminase (ALT) level of 500 U/L and aspartate transaminase (AST) level of 261 U/L.

Further laboratory workup including hepatitis serologies, antinuclear antibody level, antimitochondrial antibody level, and ceruloplasmin and alpha-1 antitrypsin levels were unremarkable. Anti-smooth muscle antibody level was 37 (normal < 20). Abdominal ultrasound revealed normal hepatic echotexture, without any evidence of portal hypertension. Tirzepatide was considered a possible cause of the liver injury, and she was recommended to discontinue the medication. Three weeks later, her ALT and AST levels had decreased to 110 U/L and 57 U/L, respectively.

The patient decided to resume tirzepatide after noticing an improvement in the liver enzyme levels. Three weeks later, an increase in both ALT and AST levels to 184 U/L and 104 U/L, respectively (Figure 1), was noted. At that point, a liver biopsy was performed,

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which revealed benign hepatic tissue with lymphocytic infiltration within the lobules and macrophage infiltration in portal tracts and sinusoidal spaces. There was no evidence of steatosis, bile duct injury, bile duct proliferation, interface hepatitis, steatosis, or necrosis on the liver biopsy (Figure 2). Her Roussel Uclaf Causality Assessment Method (RUCAM) score was 5 (Table 1). Based on her overall presentation, a diagnosis of drug-induced liver injury (DILI) from tirzepatide was made. She was recommended not to reinitiate tirzepatide. Her blood work 2 months later revealed an ALT level of 36 U/L and AST level of 24 U/L. The patient was switched to semaglutide at that time and continued to have normal liver enzyme levels on follow-up (3 months after initiating semaglutide).

DISCUSSION

To the best of our knowledge, this is the first reported case of tirzepatide-induced liver injury. In our patient, the diagnosis of tirzepatide-induced liver injury was based on the history of recent initiation of tirzepatide before presentation, improvement in liver enzyme levels after discontinuation, and an increase in liver enzyme levels after reinitiation.

The RUCAM scale used to identify if the liver injury is secondary to drug use was noted to be 5, which classified it as possible DILI.[8] We propose that the prompt recognition of the repeat elevation in liver enzyme levels and subsequent discontinuation of tirzepatide limited any further elevation in enzyme levels. As such, their levels were not allowed to rise to the threshold of doubling, which in and of itself would have resulted in a RUCAM score of 7 and pushed the likelihood of DILI into the probable range. Our patient also had mildly elevated anti-smooth muscle antibody levels. Studies have reported that it is difficult to distinguish DILI from AIH because of significant overlap in the clinical features and presence of antibodies in both the conditions. A limitation of this report is that we did not measure tirzepatide-induced or immunoglobulin G (IgG) antibodies; however, considering the lack of interface hepatitis on biopsy, the diagnosis was considered less likely.

The underlying mechanism responsible for hepatotoxicity from this drug continues to be unclear. As of this report, 3 cases of liver injury from GLP-1 agonists have been reported.[9–11] Kern et al[9] reported a case of liraglutide-induced autoimmune hepatitis. They hypothesized that liraglutide induced immune-mediated liver injury due to the formation of anti-liraglutide antibodies. Patel et al[10] and Neahusan et al[11] each reported a case of dulaglutide-induced liver injury. However, they did not comment on the mechanism of

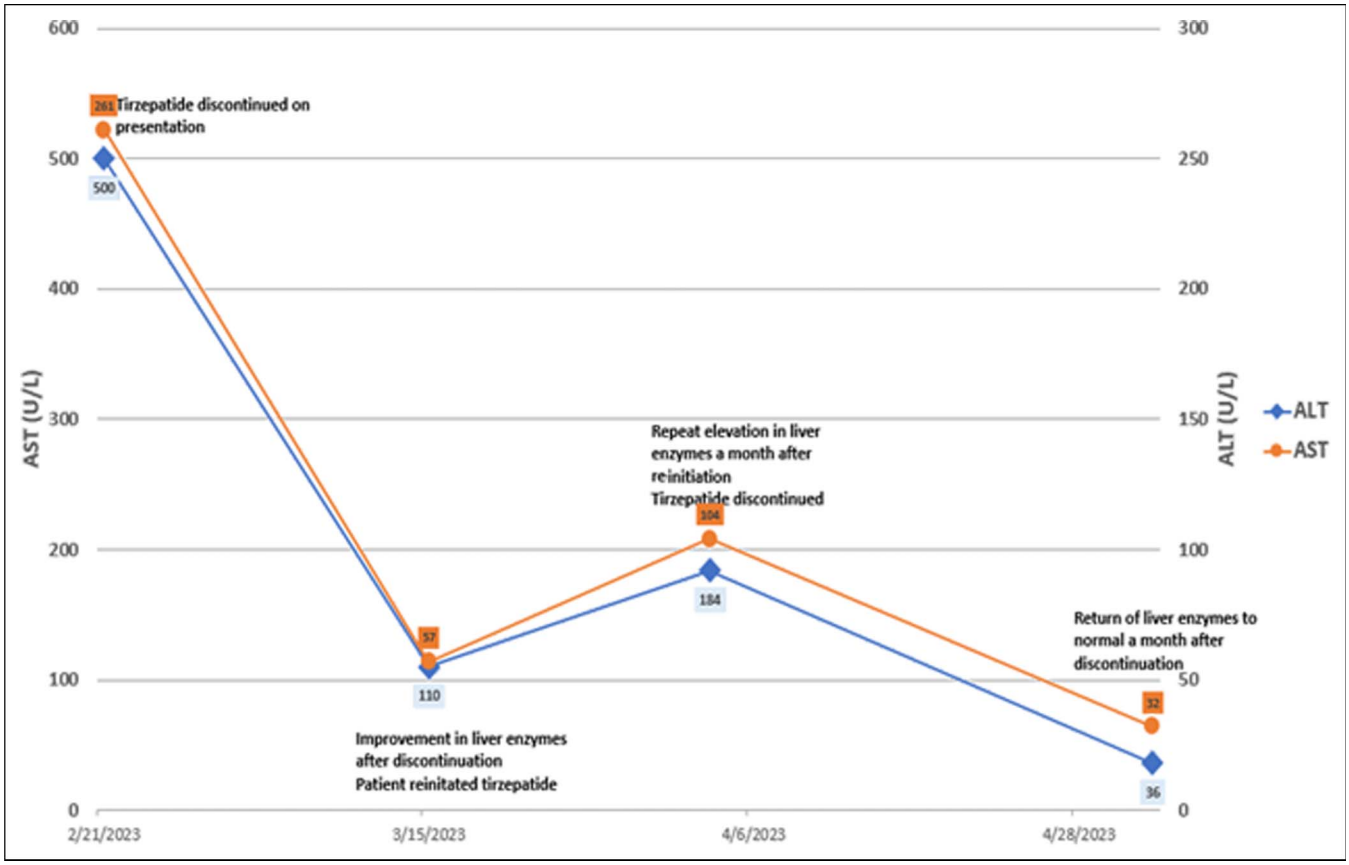

Figure 1. Temporal relation of tirzepatide use and ALT and AST patterns. ALT, alanine transaminase; AST, aspartate transaminase.

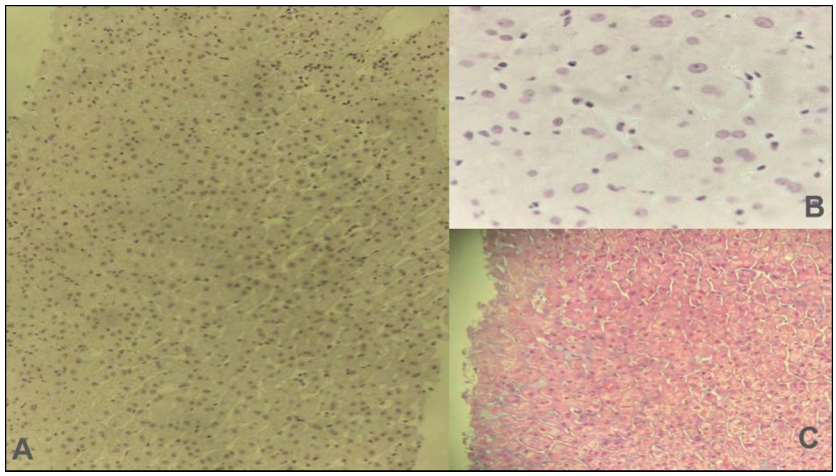

Figure 2. (A) Liver biopsy showing no evidence of fibrosis (10×). (B) Presence of macrophages on liver biopsy (40×). (C) No evidence of steatosis or inflammation on liver biopsy (10×).

hepatotoxicity. Our patient had no steatosis on liver biopsy, despite having multiple risk factors of steatotic liver disease. We hypothesize that in our patient, tirzepatide use resulted in rapid mobilization of fat from the liver and was responsible for the elevation in liver enzyme levels. This phenomenon has also been noted in an investigational drug miricorilant, a selective glucocorticoid receptor modulator that is currently under development for metabolic dysfunction-associated steatotic liver disease.[12] In their phase 2a study, 4 of 5 patients on the drug were noted to have elevation in liver enzyme levels greater than 250 IU/mL, which was associated with a rapid and marked reduction in liver fat content.[12] It was speculated that the perturbation in liver enzyme levels was related to rapid defatting of the liver.[12]

In conclusion, we report the first case of tirzepatide-induced liver injury. It is possible that as the use of this drug increases, we will note more postmarketing adverse events in the next decade. Physicians should be aware of this rare side effect, and regular monitoring of liver function tests will be beneficial in identifying patients with hepatotoxicity earlier during the course.

DISCLOSURES

Author contributions: A. Sohal and L. Casanova: writing the draft; KV Kowdley: patient evaluation, critical revisions, and is the article guarantor.

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Table 1. RUCAM score

Factors	Case	Score
Time of onset from the beginning of drug use	<90 d	2
Change in ALT levels between peak and stopping of the drug use	>50% improvement in 30 d after withdrawal	2
Risk factors		
1. Age > 55	Yes	0
2. Alcohol/pregnancy	No	0
Concomitant drug use	Unknown hepatotoxicity	0
Exclusion of other causes	Ruled out all 6 causes of group 1	1
Previous information on hepatotoxicity	Unknown	0
Response to readministration	No doubling of ALT levels with the drug readministration	0
Total score	Possible	5

ALT, alanine transaminase; RUCAM, Roussel Uclaf Causality Assessment Method.

speakers bureaus, manuscript writing, or educational events from AbbVie, Gilead, and Intercept; participation in a data safety monitoring board or advisory board for CTI, Medpace and Labcorp; stock or stock options for Inipharm; and receipt of equipment, materials, drugs, medical writing, gifts, or other services from Sonic Insight.

Informed consent was obtained for this case report.

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