CASE REPORT

Turmeric-Induced Liver Injury in a Patient with Concurrent Semaglutide Use

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ABSTRACT

Turmeric has surged in popularity as one of the most widely used dietary supplements in the United States. Recognized for its anti-inflammatory and antioxidant properties, it has traditionally been regarded as safe. Recent literature and reports in LiverTox have documented over a dozen cases of acute liver injury associated with the use of turmeric supplements. However, potential drug interactions with turmeric have been described but not well-documented. Thus, we present a case of drug-induced liver injury (DILI) correlated with turmeric supplement use and the concurrent use of semaglutide.

INTRODUCTION

Drug-induced liver injury (DILI) from herbal and dietary supplements (HDS) in the United States has increased as the usage of HDS has become more popular. According to the United States Drug-Induced Liver Injury Network (DILIN), approximately 20% of cases of DILI can be attributed to HDS, an increase from 7% in 2004.[1]

Turmeric supplements have become one of the top selling HDS in the United States. It is promoted for arthritis, pain, and digestive disorders. Common side effects include dermatitis and gastrointestinal upset, while instances of hepatotoxicity are rare. Different formulations that increase the bioavailability of curcumin, the active ingredient in turmeric, have been linked to cases of liver injury and acute hepatitis outbreaks outside of the United States.[2]

Possible interactions between turmeric and other drugs, such as anticoagulants, antiplatelets, antidiabetics, and chemotherapeutic agents, have been described in *in vitro* and animal studies, but have not been well studied in humans.[3] In this report, we describe a possible drug interaction in a patient who had been using turmeric supplements and semaglutide injections and presented with elevated liver transaminases and bilirubin, with improvement upon cessation of the supplement.

CASE PRESENTATION

A 70-year-old female with coronary artery disease (status post drug-eluting stent x 2 10 years ago), hypertension, type 2 diabetes mellitus, rheumatoid arthritis, chronic

obstructive pulmonary disease, and remote history of bladder cancer presented to the emergency department with two weeks of nausea, jaundice, dark colored urine, loss of appetite, and clay-colored stool. On admission, the patient's vitals were unremarkable. Her height was 127 cm and weight was 105.9 kg (body mass index 42.7 kg/m^2). The physical exam was notable for scleral icterus, bilateral palmar erythema, and jaundice. She had no signs of encephalopathy or ascites and was alert and oriented to person, place, and time. The patient denied any recent alcohol or acetaminophen use and had no history of excessive alcohol use. She also denied any history of prior liver disease, recent travel, or sick contacts.

Two months prior to her admission, the patient had started taking semaglutide 2 mg/3mL injection pens for weight loss and over the counter turmeric supplements for her rheumatoid arthritis, in addition to her other existing medications (**Table 1**). She had been consuming two 1500mg capsules per day until the day of hospital admission. Ingredients of the supplement were listed as "1500mg turmeric root extract," with "95% curcuminoids," "100mg organic ginger root powder," and "10mg of black pepper." Upon admission, the semaglutide and turmeric supplements were stopped, along with any of her other medications that could be hepatotoxic, including spironolactone, sertraline, nortriptyline, and temazepam.

On admission, laboratory workup was remarkable for aspartate transaminase (AST) 912 U/L, alanine aminotransferase (ALT) 999 U/L, alkaline phosphatase 409 U/L, and total bilirubin 20.5 mg/dL. Platelet count was 235 k/mm^3, INR 1.5, and albumin 2.6 g/dL. Phosphatidylethanol and acetaminophen levels were undetected. Acute hepatitis serologies, HIV and cytomegalovirus serologies, serum ceruloplasmin, anti-smooth muscle antibody, antimitochondrial antibody, immunoglobulin levels, α-fetoprotein, HFE gene, and α-1 antitrypsin levels were all unremarkable (**Table 2**).

Abdominal ultrasound with Doppler demonstrated patent hepatic and portal vasculature. Computed tomography of the abdomen and pelvis showed normal liver size, cholelithiasis with diffuse gallbladder wall thickening, and no bile duct dilation. Magnetic resonance imaging of the abdomen showed slightly nodular contour, suggesting cirrhosis, with no suspicious focal liver lesion. There were multiple intraductal papillary mucinous neoplasms measuring up to 5mm in the pancreas, and an otherwise unremarkable pancreatobiliary system. A liver biopsy performed on day two of hospitalization revealed marked, lobular, predominantly lymphomononuclear inflammatory infiltrate involving the hepatic sinusoids; milder portal inflammatory infiltrates; and marked lobular disarray in the hepatocytic parenchyma with areas of hepatocytic swelling and scattered acidophil bodies, consistent with a cholestatic pattern of DILI.

During the hospitalization, liver transaminases down-trended with supportive therapy, but total bilirubin increased and peaked at 26.4 mg/dL (**Figure 1**). Mental status was intact throughout the hospital course. The patient was discharged once bilirubin levels remained stable, and liver function tests and bilirubin were monitored through serial bloodwork in an outpatient setting. On discharge, AST was 66 U/L, ALT was 91 U/L, Alkaline phosphatase was 318 U/L, and total bilirubin was 21 mg/dL. Subsequent outpatient blood work showed continued improvement (**Figure 1**).

Table 1: Patient's Medications Prior to Admission and at Discharge

Medications Prior to Admission	Medications at Discharge
Nortriptyline 10 mg, oral tablet once a day	Albuterol 90 mcg, 2 puffs every 4 hours
Sertraline 100 mg, oral tablet once a day	Aspirin 81 mg oral tablet once a day
Temazepam 30 mg, oral tablet once a day	Carvedilol 6.25 mg oral tablet twice a day
Aspirin 81 mg, oral tablet once a day	Clopidogrel 75 mg oral tablet once a day
Carvedilol 6.25 mg, oral tablet twice a day	Insulin Novolog 30 units, subcutaneous every 12 hours
Spironolactone 25 mg, oral tablet once a day	Semaglutide 2 mg, subcutaneous every week
Valsartan 320 mg, oral tablet once a day	Umeclidinium 62.5 mcg, 1 inhale every 24 hrs
Insulin Novolog 20 units, subcutaneous three times a day	
Lantus 60 units twice a day	
Umeclidinium 62.5 mcg, 1 inhale every 24 hrs	
Meloxicam 15 mg, one tablet once a day	
Semaglutide 2 mg/3mL injection pens, subcutaneous once weekly	
Turmeric supplements 1500 mg, one tablet twice a day	

Figure 1. Trend of ALT, AST, Alkaline phosphatase, and Total Bilirubin.

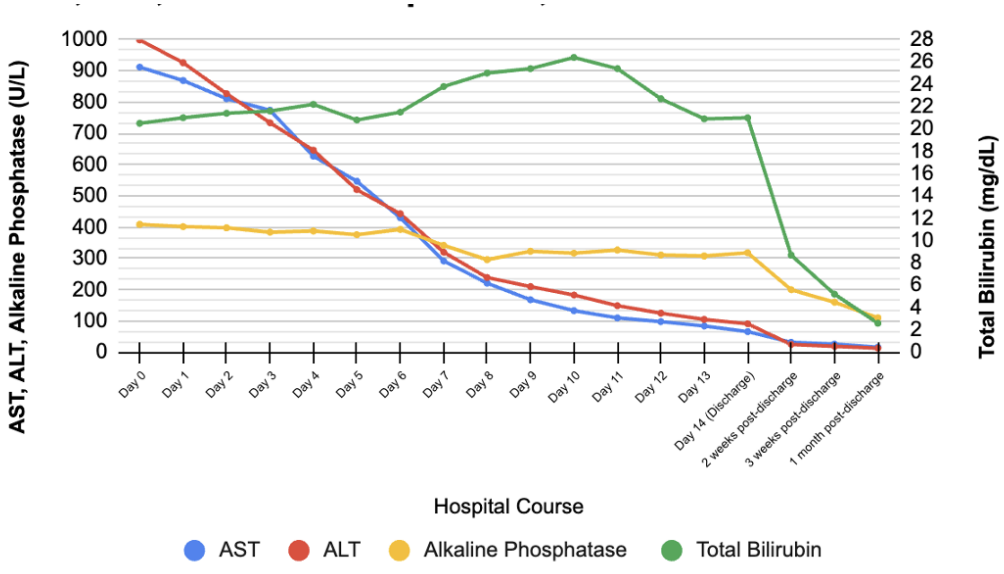

Table 2: Other lab values from workup

Test	Value	Reference Range
Hepatitis A Ab, IgM	Non reactive	Non reactive
Hepatitis A Ab, IgG	Negative	Negative
Hepatitis B Core Ab, IgM	Negative	Negative
Hepatitis B Virus DNA (IU/mL)	Not detected	Not detected
Hepatitis B Surface Antibody	Non reactive	Non reactive
Hepatitis B Surface Ag	Non reactive	Non reactive
Hepatitis C Virus Antibody	Non reactive	Non reactive
Hepatitis C Virus RNA (IU/mL)	Not detected	Not detected
Hepatitis E Antibody, IgM	Not detected	Not detected
Herpes Simplex Virus Type 1 IgG Ab	Positive	Negative
Herpes Simplex Virus Type 2 Ab, IgG	Negative	Negative
HIV Ag/Ab	Non reactive	Non reactive
SARS-COV-2 RNA RT-PCR	Not detected	Not detected
Epstein Barr Virus VCA Ab, IgM (U/mL)	<10	<36
Epstein Barr Virus Nuclear Ag IgG (U/mL)	157	<18
Epstein Barr Virus Viral Capsid Antigen IgM Ab	negative	negative
Cytomegalovirus DNA (IU/mL)	Not detected	Not detected
Ceruloplasmin, Serum (mg/dL)	34	16-45
Anti-Smooth Muscle Antibody	<1:20	Negative or less than 1:20
Liver/Kidney Microsome T1 Ab (U)	<5.0	<5.0
Soluble Liver Ag Ab (U)	1.2	0-24.9
IgG (mg/dL)	1033	528-1736
Iron (mcg/dL)	162	40-145
Ferritin (UG/L)	281.6	9-120
Total Iron Binding Capacity (mcg/dL)	274	275-365
Transferrin saturation (%)	59	<45
Lipase (U/L)	29	8-78
Amylase (U/L)	20	22-100

Table 3: RUCAM Causality Assessment of the Case

Hepatocellular Pattern		**Score**
Time to Onset • From beginning of drug use	5-90 days	**+2**
Course • Change in ALT between peak value and ULN after stopping the drug	Decrease >50% within 8 days	**+3**
Risk Factors • Alcohol or Pregnancy • Age of the patient	 Absence Age > 55 years	 **0** **+1**
Concomitant Drugs	Concomitant drug with suggestive or compatible time to onset	**-1**
Exclusion of other causes of liver injury	All non-drug causes ruled out	**+2**
Previous information on hepatotoxicity of the drug	Reaction published but unlabeled	**+1**
Response to readministration	Not done	**0**
	Total	**8**

Abbreviations used: ALT, alanine aminotransferase; ULN, upper limit of the normal range of values

DISCUSSION

DILI is considered a diagnosis of exclusion that is based on the results of a complete hepatic workup for other causes of acute liver injury and patient medical history. In our patient, liver biopsy further supported the diagnosis of DILI. The R ratio was calculated to be 6.7, suggesting hepatocellular injury, and is within the range of R ratios (R value range 3.4-42.8) reported by DILIN for turmeric-induced liver injury.[4] The Roussel Uclaf Causality Assessment Method (RUCAM) score for this patient was 8 (**Table 3),** indicating it was "probable" that turmeric caused her liver injury.[5]

There has been one reported case in 2022 describing a 51-year-old man who developed simultaneous cholestatic DILI and nephritis due to oral semaglutide, but there have been no reported cases of liver injury due to subcutaneous semaglutide.[6] According to LiverTox, there have been increased reports of liver injury associated with higher bioavailable forms of turmeric supplements that have more commonly resulted in a hepatocellular pattern of liver injury, in which there are disproportionate elevations in serum aminotransferases when compared to alkaline phosphatase and serum bilirubin.[2] Furthermore, the Food and Drug Administration's drug-induced liver injury severity and toxicity (DILIst) binary classification for curcumin is 1, indicating a "DILI positive" result and a concern for DILI.[7] In contradistinction, our patient presented with a cholestatic pattern of liver injury that was described and confirmed by pathology. The discrepancy between our patient's pathological finding and initial R ratio, which identified the injury pattern as hepatocellular, may indicate a limitation in

the calculation of the R ratio or in the thresholds used to classify liver injury.[1] Alternatively, this discrepancy can also be due to hepatocellular damage occurring earlier in the disease process, potentially related to turmeric's mechanisms of action that are not yet fully understood. In addition, her bilirubin and alkaline phosphatase elevations were more persistent compared to transaminase elevations, with transaminase levels decreasing rapidly after cessation of the drug, more consistent with cholestatic liver injury **(Figure 1).**

Given her body weight (105.9 kg), our patient was taking a very high dose of the turmeric supplement (3000 mg/day) that contained 95% curcumin, greater than the World Health Organization's determined acceptable daily intake of 3 mg/kg body weight/day of curcumin, which may suggest a dose-dependent injury.[8] Our patient's turmeric supplement was formulated with black pepper (piperine). Piperine increases the bioavailability of curcumin up to 2000% by inhibiting CYP3A, leading to greater absorption in the liver and precipitating liver toxicity.[9,10] Notably, there may be an immune-mediated component to the mechanism of turmeric-induced liver injury. The carriage of the HLA-B*35:01 allele has been found to be closely associated with hepatic injury from turmeric and other herbs containing polyphenols, possibly due to an interaction between curcumin and the HLA molecule leading to self-antigen recognition by T cells on liver cells.[2] However, our patient was not tested for this allele, so it is unknown whether this mechanism contributed to her liver injury. Our patient's concurrent use of turmeric supplements and semaglutide may have further contributed to the development of liver injury. Semaglutide, a GLP-1 analogue, has been found to delay gastric emptying and inhibit duodenal and small intestine mobility.[11] This could further increase curcumin bioavailability in the body. Both turmeric and semaglutide have been shown to inhibit the activation of the nuclear factor (NF)-κB signaling pathway, which regulates inflammation in the liver by balancing both proinflammatory and anti-apoptotic responses to pathogens.[12-14] Dysregulation of this pathway can result in spontaneous liver injury, fibrosis, and hepatocellular carcinoma.[14] The use of both substances could have potentiated each other's inhibitory effects, contributing to the severity of the DILI.

This case report adds to the growing number of incidents of turmeric-induced acute liver injury and proposes a possible drug interaction with semaglutide on the liver. With the growing popularity of turmeric supplements and semaglutide use in the United States, there is a need for more *in vivo* studies to be conducted to investigate the interaction between turmeric supplements with semaglutide and other conventional drugs.

Notes

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