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CASE REPORT | LIVER

Autoimmune Hepatitis Associated With Turmeric Consumption

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ABSTRACT

Turmeric is a popular herbal dietary supplement that has been considered safe and even shown to have hepatoprotective properties. In the recent times, however, there have been a few case reports of turmeric-induced liver injury. We report a 55-year-old woman with chronic turmeric consumption whose initial diagnosis was acute autoimmune hepatitis. She declined steroid treatment, and hence, we recommended discontinuing her long-term turmeric usage. A month after discontinuation, her liver function returned to normal. This case demonstrates the importance of recognizing the potential adverse effects of herbal dietary supplement.

INTRODUCTION

Turmeric was the top-selling herbal supplement for the fourth consecutive year with sales of $47,654,008 in 2016.[1] Increased popularity is because of turmeric's purported anti-inflammatory, antioxidant, wound healing, antimicrobial, and antineoplastic properties.[2] Its therapeutic effects on the liver have been documented.[3,4] Favorable results have been shown in the management of cholestasis, hepatotoxicity, hepatic fibrosis, and hepatic cancers.[4–6] Nonetheless, a few case reports have associated turmeric intake with severe hepatitis. This case is unique because our patient presented with classic autoimmune hepatitis (AIH) features after turmeric use. It serves to highlight the importance of history taking that includes thorough evaluations of potential herbal dietary supplement (HDS) usage.

CASE REPORT

A 55-year-old woman with a medical history of Hashimoto's thyroiditis presented to the urgent care with a chief complaint of nausea, vomiting, dark urine, and jaundice for 3 weeks. Her symptoms started at her son's wedding after a couple of drinks of vodka and cranberry juice. She denied alcohol abuse. She was on famotidine 20 mg tablet by mouth daily, aluminum hydroxide-magnesium hydroxide-simethicone 200 mg-200 mg-20 mg/5 mL of oral suspension 10 mL by mouth as needed, levothyroxine 50 μg by mouth daily, and Qunol Liquid Turmeric 15 mL daily. On physical examination, she was alert and oriented to person, place, and time with no asterixis. The only positive finding was scleral icterus. Laboratory studies showed a normal international normalized ratio (INR) of 1.0 and normal thyroid stimulating hormone level of 2.18 μIU/mL but were significant for elevated total bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) of 11.8 mg/dL, 204 U/L, 2743 U/L, and 2353 U/L, respectively. Right upper quadrant ultrasound and abdominal and pelvis computed tomography showed no abnormalities. The patient was admitted to the hospital for further workup.

Infectious viral etiologies (hepatitis A/B/C/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus-1, and herpes simplex virus-2) were negative. Urine drug screening and acetaminophen levels were unremarkable. Antinuclear antibodies (ANA) were positive positive with a titer of 1:80 but anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), anti-double stranded DNA antibody (anti-dsDNA), and anti-liver-kidney microsomal antibody type 1 (anti-LKM-1) were normal. Tests for Wilson disease, alpha-1-antitrypsin deficiency, and hemochromatosis were negative. Magnetic resonance cholangiopancreatography showed no anomalies. Doppler ultrasonography was negative for hepatic and portal vein

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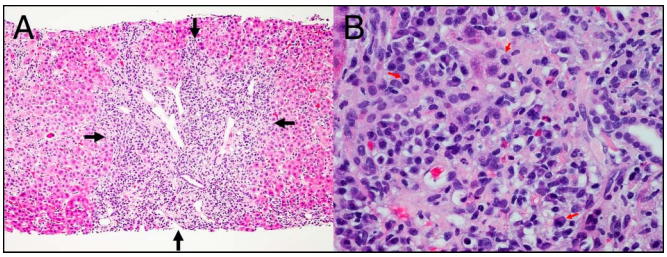

Figure 1. Hematoxylin & eosin stain of the liver with portal triad at (A) 100× magnification showing moderate inflammation of portal triads with interface hepatitis (black arrows). Hematoxylin & eosin stain of the liver with portal triad at (B) 400x magnification showing a mixture of plasma cells (red arrows), lymphocytes, eosinophils, and neutrophils. Plasma cells are typical findings of autoimmune hepatitis.

thrombosis. Differential diagnosis was drug-induced liver injury vs AIH, and the patient underwent a liver biopsy. After the patient's symptoms resolved, she was discharged with close outpatient follow-up.

The patient was seen in the liver clinic a week after. Her INR continued to stay normal at 1.0. Her liver enzymes were improved but still showed elevated total bilirubin (3.1 mg/dL), ALP (148 U/L), ALT (1062 U/L), and AST (635 U/L). Her repeat ANA, however, increased to 1:320. Liver biopsy showed interface hepatitis with a mixture of plasma cells, lymphocytes, eosinophils, and neutrophils (Figure 1). Using the revised original scoring system of the International Autoimmune Hepatitis Group, the score was 18 (definite diagnosis of AIH) (Table 1).[7] Treatment options of steroid induction or immunosuppressive therapy were discussed, but the patient refused. Her medication list was reviewed again. Turmeric supplement that she started 3 months ago for purported health benefits was discontinued. After a month, her symptoms resolved and her blood tests improved, most decreasing to within normal limits (total bilirubin 2.1 mg/dL, ALP 47 U/L, ALT 31 U/L, AST 34 U/L, and ANA < 1:80). The calculated Roussel Uclaf Causality Assessment Method (RUCAM) score that assesses the causal role of drugs (in this case, turmeric) in liver injury was 9, highly probable adverse drug reaction because of turmeric (Table 2).[8]

Table 1. Revised scoring system of the International Autoimmune Hepatitis Group[a]

Criteria	Points	Our case
Sex		
Female	2	X
ALP: AST (or ALT) ratio		
>3	−2	
<1.5	2	X
IgG (or gamma-globulin) level above normal		
>2	3	
1.5–2	2	
1–1.5	1	
<1	0	
ANA, ASMA, or anti-LKM1 titers		
>1:80	3	X
1:80	2	
1:40	1	
<1:40	0	
AMA		
Positive	−4	
Viral markers		
Positive	−3	
Negative	3	X
Drugs		
Yes	−4	
No	1	X
Alcohol		
<25 g/d	2	X
>60 g/d	−2	
HLA		
DR3 or DR4	1	
Immune disease		
Thyroiditis, colitis, others	2	X
Other markers		
Anti-SLA, anti-actin, anti-LC1, pANCA	2	
Histological features		
Interface hepatitis	3	X
Plasmacytic	1	
Rosettes	1	
None of the above	−5	
Biliary features	−3	
Other features	−3	
Treatment response		
Complete	2	
Relapse	3	
Total		18

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibodies; anti-LC1, anti-liver cytosol antibody type 1; anti-LKM1, anti-liver-kidney microsomal antibody type 1; Anti-SLA, anti-soluble liver antigen antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; HLA, Human leukocyte antigen; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies.

[a]Revised Scoring System of the International Autoimmune Hepatitis Group adapted from Manns et al.[2] Pretreatment aggregate score >15 indicates definite diagnosis of AIH. Aggregate score of 10–15 is a probable diagnosis of AIH. Patient's score of 18 indicates AIH as a cause of liver dysfunction.

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Table 2. Roussel Uclaf Causality Assessment Method (RUCAM) for drug-induced liver injury[a]

Criteria	Points	Our case
Time to onset from beginning of drug/herb		
5–90 days (rechallenge: 1–15 days)	2	
<5 or >90 days (rechallenge: >15 days)	1	X
Time to onset from cessation of drug/herb		
≤15 days (except for slowly metabolized chemicals >15 days)	1	
Course of ALT after cessation of drug/herb (% difference between ALT peak and ULN)		
Decrease ≥50% within 8 days	3	X
Decrease ≥50% within 30 days	2	
No information or continued drug use	0	
Decrease ≥50% after 30th day	0	
Decrease <50% after the 30th day or recurrent increase	−2	
Risk factors		
Alcohol use—presence	1	X
Alcohol use—absence	0	
Age ≥ 55 years	1	X
Age < 55 years	0	
Concomitant drug(s)/herb(s)		
None or no information	0	X
Concomitant drug/herb with incompatible time to onset	0	
Concomitant drug/herb with compatible or suggestive time to onset	−1	
Concomitant drug/herb known as hepatotoxin and with compatible or suggestive time to onset	−2	
Concomitant drug/herb with evidence for its role in this case (positive re-challenge or validated test)	−3	
Search for alternative causes[b]		
All causes reasonably ruled out (group I and II)	2	X
Six causes of group I ruled out	1	
4–5 causes of group I ruled out	0	
<4 causes of group I ruled out	−2	
Alternative cause highly probable	−3	
Previous hepatotoxicity of drug/herb		
Reaction labeled in the product characteristics	2	
Reaction published but unlabeled	1	X
Reaction unknown	0	
Responses to unintended re-exposure		
Doubling of ALT with drug/herb alone, (if ALT <5 times ULN before re-exposure)	3	
Doubling of ALT with drug/herb already given at time of first reaction	1	
Increase of ALT but <5 times ULN in the same conditions as for first administration	−2	
Other situations	0	
Total		9

ALT, alanine aminotransferase; ULN, upper limit of normal.
[a]RUCAM for drug-induced liver injury adapted from Danan and Benichou.[17]
[b]Group I causes are hepatitis A virus, hepatitis B virus, hepatitis C virus, biliary obstruction (imaging), alcoholism, and acute recent hypotension. Group II causes are complications of underlying disease such as sepsis, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus. Total score indicates the probability of adverse reaction as follows: ≥9: highly probable, 6–8: probable, 3–5: possible, 1–2: unlikely, and ≤ 0 excluded. Patient's score of 9 indicates highly probable adverse reaction from turmeric.
Reprinted from *Journal of Clinical Epidemiology*, with permission from Elsevier. Danan G, Benichou C. Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: Application to drug-induced liver injuries. *Jnl Clin Epidemiol* 1993:46(11);1323-30.

DISCUSSION

Curcumin (diferuloylmethane) is the component of turmeric that provides health benefits.[9] Yet, it has low bioavailability in its pure form.[10,11] Consequently, about a quarter of the US turmeric drug supplement contains piperine, a major active component of black pepper that has been associated with an increase of 2000% in the bioavailability of curcumin.[12,13] Given its complex pharmacokinetics, its safety has been questioned. Numerous clinical trials have shown that curcumin is well tolerated, with some studies recommending targeted doses of 4,000–8,000 mg.[14,15] Recently, however, case reports have shown turmeric's deleterious effects on the liver.

Lukefahr et al described a 71-year-old woman with multiple comorbidities who was diagnosed with AIH that resolved after discontinuation of turmeric.[16] Although the hepatic injury was associated with turmeric, the authors raised a possibility that polypharmacy could have contributed to pharmacokinetics or pharmacodynamics of turmeric and caused the hepatocellular injury. Moreover, they commented that many turmeric supplements contain other additional chemicals such as piperine, and those compounds may alter metabolism with concurrent medications, possibly augmenting the risk of liver damage.

Luber et al reported a 52-year-old woman with a sole history of oligoarticular osteoarthritis on occasional diclofenac and turmeric supplementation, who was discharged from the hospital with a diagnosis of diclofenac-induced liver injury.[17] Postdischarge, she resumed her turmeric supplementation and developed acute hepatitis that resolved with cessation. The patient's turmeric supplementation was analyzed for

purity and was tested negative for drugs, adulterants, or toxic heavy metals. The authors concluded that pure turmeric could directly lead to liver damage but stated that unknown contaminants causing hepatic injury could not be excluded.

Similar to the report by Lukefahr et al, this case report raises the possibility that turmeric can present with AIH. As deliberated by Luber et al, we considered other compounds that could have been added to turmeric. We found 2 notable active ingredients: black pepper extract and luo han guo (LHG). We cannot rule out the possibility that black pepper extract could have contributed to hepatotoxicity. LHG's possibility as a hepatotoxic agent has not been discussed in the literature. LHG has been used for hundreds of years in China as a natural sweetener and a traditional home remedy for its antitussive, antiasthmatic, antioxidation, liver-protection, glucose-lowering, immunoregulation, and anticancer effects.[18] The US Food and Drug Administration has characterized LHG as generally safe, although this has been controversial because of a lack of evidence.[19] Accordingly, more research into LHG is needed to elucidate its safety as an additive. In conclusion, it is important to recognize that AIH can mimic drug-induced liver injury as in our patient with turmeric supplementation. Healthcare providers must take a thorough history that includes the usage of HDS and its additives. It is essential to keep in mind that HDS has the potential to cause harmful side effects.

DISCLOSURES

Author contributions: BS Lee wrote and revised the manuscript. T. Bhatia revised the manuscript and is the article guarantor. CT Chaya, R. Wen, and BS Lim revised the manuscript. MT Taira provided the pathology images.

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