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CASE REPORT

Turmeric-induced Liver Injury

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Abstract

The use of herbal and dietary supplements has gained an increasing foothold in the United States. While often touted as safer alternatives to more traditional "western" therapeutics, the pharmacology and pharmacokinetics of these substances, their interactions with other medications, their purity, and individual pharmacogenomics, remain unknown. Turmeric is a popular supplement that has been demonstrated to be safe, and even hepatoprotective. Recently, however, there have been several reports of turmeric-induced liver injury. We report a case of drug-induced liver injury due to turmeric that was complicated by acute liver failure and hepatorenal syndrome.

Keywords: Turmeric, DILI, Liver injury

1. Introduction

Herbal and dietary supplements have become increasingly popular, with at least half of the US population using some form of supplementation.[1] Turmeric is the second most common herbal supplement in the United States.[2] The volatile oils and curcuminoids found in turmeric rhizomes are considered to be the active components and are collectively referred to as curcumin.[3] Turmeric has gained attention for its antioxidant, anti-inflammatory, and anti-cancer properties.[4] Randomized controlled trials have indicated that curcumin treatment is considered safe with minimal reports of severe side effects.[5-9]

Drug-induced liver injury (DILI) is a frequently encountered adverse drug reaction associated with certain medications and herbal supplements[10]; the spectrum of injury ranges from mild transaminitis to acute liver failure. DILI-associated jaundice and elevated serum aminotransferases above three times the upper limit of normal portend a poor prognosis with a mortality rate of 14%.[11-14] DILI is a complex process involving the parent drug, its associated metabolites, and their complex interaction with host genetics and immune responses.[15] DILI may be categorized into intrinsic and idiosyncratic patterns. Intrinsic hepatotoxicity is a dose-dependent and predictable reaction that results in mitochondrial inhibition and formation of mitochondrial permeability transition pores, leading to mitochondrial dysfunction, reduced ATP production, and elevated levels of reactive oxygen species.[16,17] On the other hand, idiosyncratic hepatotoxicity is unpredictable and dose-independent, it is influenced by a combination of host genetic, immunologic, metabolic, and drug factors in a mechanism that remains uncertain.[16,17]

2. Case presentation

A 66-year-old African American female presented to the emergency department with two weeks of icterus, nausea, decreased appetite, light-colored stool, and dark urine. She rarely consumed alcohol and had no history of tattoos, illicit drug use, or recent travel. Her medical history was notable for peripheral arterial disease, stage two chronic kidney disease, and a newly diagnosed breast cancer awaiting chemotherapy initiation. She was hemodynamically stable, and examination revealed a well-appearing female who was noticeably jaundiced, without features of chronic liver disease.

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Laboratory diagnostics were remarkable for elevated total bilirubin (29 mg/dL, reference range 0.2–1.1 mg/dL) that was predominantly direct (21.48 mg/dL; reference range 0.0–0.3 mg/dL) and elevated liver enzymes (alanine aminotransferase (ALT) 738 U/L, reference range 10–49U/L; aspartate aminotransferase (AST) 840 U/L; reference range 0–33 U/L), alkaline phosphatase (ALP) 397U/L; reference range 46–116 U/L, INR1.8 (reference range 0.8–1.2). R-factor was 4.3 (where R = [ALT/ULN] ÷ [ALP/ULN]; R ≥ 5 is hepatocellular, 2< R < 5 is mixed, and R < 2 is cholestatic injury), indicating a mixed hepatocellular and cholestatic liver injury.

Further history revealed that six months prior to presentation, the patient started taking a half-teaspoon of ground turmeric as an herbal remedy from a local herbal store. One month later, routine blood work demonstrated elevated liver enzymes (ALT 275U/L, AST 178U/L, ALP 178U/L) and a follow-up liver ultrasound showed fatty infiltration. Turmeric was discontinued, and one month later liver enzymes improved (ALT 77U/L, AST 81U/L) though ALP remained persistently elevated (ALP 313U/L) (Fig. 1). Unfortunately, the patient resumed turmeric supplementation. Long-term medications included metoprolol, amlodipine, hydralazine, lisinopril, atenolol, chlorthalidone, aspirin, clopidogrel, and atorvastatin, unchanged for at least a year.

On admission, all oral medications and supplements were discontinued. Further diagnostic workup including acute hepatitis panel as well as antibodies (liver-kidney, anti-mitochondrial, anti-smooth muscle, and antinuclear) were negative. Low Complement C3 and C4 and normal immunoglobulins (IgA, IgG, and IgM) were also noted. Serum eosinophil counts, copper and ceruloplasmin, iron studies, and alpha-1 antitrypsin were all within normal limits. Acetaminophen and salicylate levels were undetectable. Liver ultrasonography demonstrated patent portal and hepatic veins with no evidence of biliary ductal dilatation. Unfortunately, by the 5th day of hospital admission, laboratory diagnostics failed to demonstrate evidence of improvement (Total bilirubin 23.3 mg/dL, ALT 644U/L, AST 841U/L, ALP 286U/L, INR 2.0) and a liver biopsy was performed; histology demonstrated a cirrhotic liver with a mixed inflammatory infiltrate, bile ductular reaction, and hepatocellular necrosis (Fig. 2). Drug-induced injury was the favored differential.

The patient's hospital course was complicated by a worsening INR and hepatic encephalopathy (INR 2.7; Ammonia 206 μmol/L; reference range 11–32 μmol/L), consistent with acute liver failure, as well as progressively worsening renal function complicated by anuric renal failure and anion gap metabolic acidosis, presumed to be secondary to hepatorenal syndrome type 1. This led to profound bradycardia and hypotension responsive to dopamine infusion and dialysis was initiated. Despite maximal medical therapy, the patient continued to worsen, and the family made the difficult decision to make her comfort care; within hours the patient passed away.

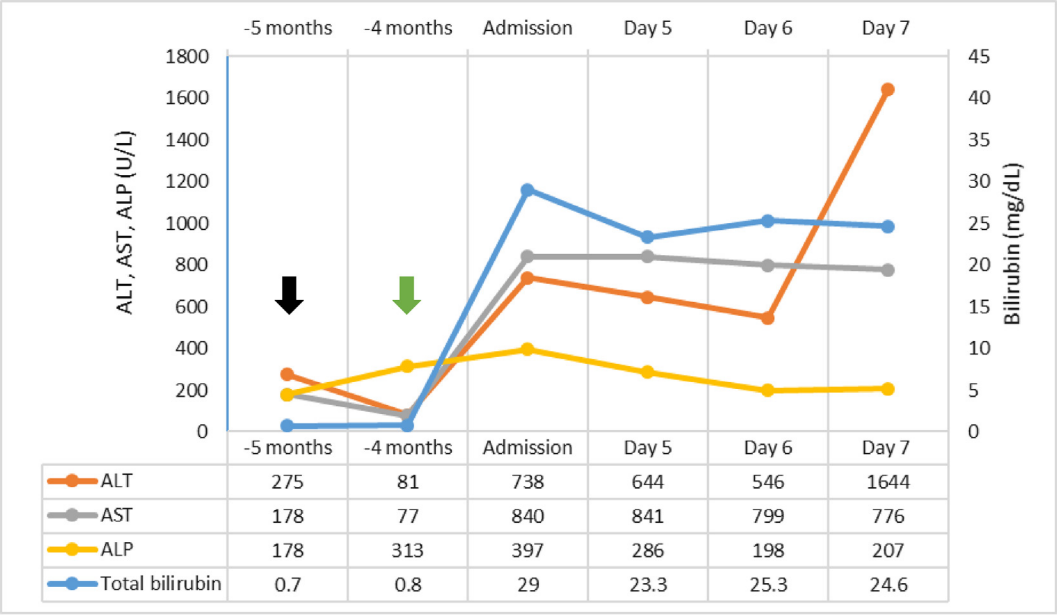

Fig. 1. Graphic distribution of liver functions tests. Trend in liver function tests pre-hospitalization and during the patient hospital course. Initial elevation of liver enzymes (black arrow). Improvement of liver enzymes upon temporary discontinuation of turmeric use (green arrow).

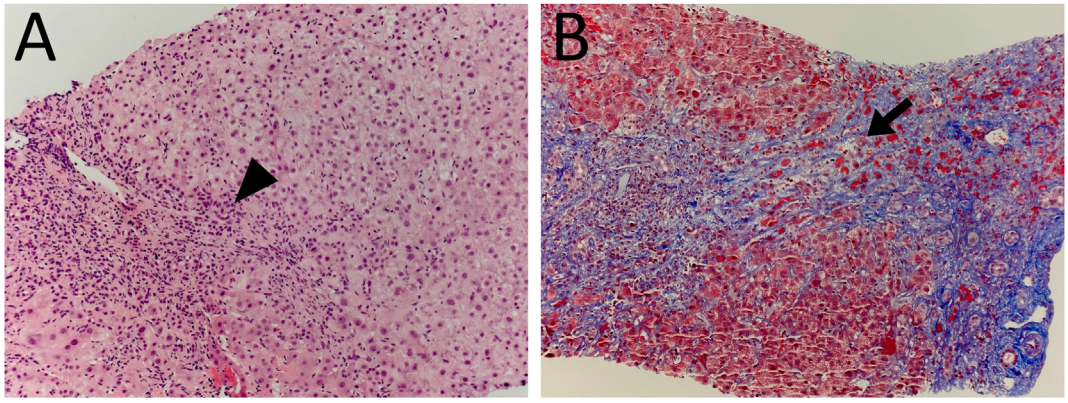

Fig. 2. Histopathology (A) Hematoxylin and eosin staining (40x magnification) demonstrated abundant inflammatory cells and necrosis in association with the central vein (arrowhead). (B) Trichrome staining (40x magnification) demonstrated evidence of bridging fibrosis (arrow).

3. Discussion

Drug-induced liver injury (DILI) refers to liver damage resulting from using specific medications, herbs, or foreign substances, leading to abnormal liver tests or impaired function. It is diagnosed after reasonable exclusion of other potential causes of liver injury.[17] Approximately 14–19 cases are reported per 100,000 people, with jaundice in 30% of cases; DILI accounts for 3–5% of hospital admissions for jaundice.[18] The sequelae of DILI range from asymptomatic elevation in liver enzymes to acute liver failure.[10] DILI may be hepatocellular, cholestatic, or mixed based on the patterns of liver enzymes abnormalities and the calculated R-factor, which is further classified into two types: intrinsic or idiosyncratic, with the latter comprising the majority of cases. The underlying mechanisms of idiosyncratic DILI remain inadequately understood, however, it is hypothesized to result from intricate interactions involving drug-related factors such as dosage, treatment duration, hepatic metabolism, lipophilicity, and host-related factors including age, gender, and genetic polymorphisms.[19]

It has been reported that taking up to 6 g of curcumin per day for 4–7 weeks is considered safe.[20] One of the reasons for this is the relatively low water solubility of curcumin, which restricts its absorption in the digestive tract. Intriguingly, multiple studies have demonstrated the ability to manipulate curcumin solubility and bioavailability.[4,21] In addition, combining curcumin with other substances such as black pepper or lecithin also increase absorption.[4,21] Remarkably, when taken with black pepper, curcumin bioavailability increases by 2000%,[22] consequently increasing the likelihood of liver injury. In our case, it was challenging to quantify the exact dose of turmeric and whether the patients' formulation was pure or mixed with other ingredients. Unfortunately, most herbal substances remain unregulated and various studies have raised concerns about turmeric adulteration in the United States. For example, New York City's health department implemented a testing initiative from 2008 to 2017, examining around 252 turmeric samples, and discovered detectable lead levels in nearly half of the turmeric samples,[23] with similar studies conducted in Boston[24] and North Carolina.[25]

Demographic characteristics are known to play a role in DILI. For instance, women are more prone to DILI compared to men.[26] Gender-related disparities can be attributed to several causes, including hormonal status, body weight, body composition, cardiac output, and gender-specific variations in the immune system, with clear evidence of subtle gender-dependent differences in metabolism mediated by the CYP3A and CYP1A2 enzymes.[26] Cytochrome P450 (CYP) activity declines with aging, and conjugation reactions have been demonstrated to be diminished in frail older adults, although this phenomenon is not consistently observed.[27,28] Additional studies have reported racial disparities in the presentation and prognosis of DILI. In one study involving approximately 1000 DILI patients, it was found that African American individuals were more susceptible to severe cutaneous reactions, severe liver injury, and worse disease outcomes (such as liver transplantation or liver-related death) in comparison to White patients.[29] A multitude of genetic polymorphisms in the CYP isoenzymes, human leukocyte antigens (HLA) alleles, and other enzymes involved in drug processing have been identified and linked to DILI.[30] A study published by the DILI network (DILIN) has found that the HLA-B*35:01 human haplotype may increase the risk of liver injury due to turmeric.[31]

The relationship between underlying liver disease and its predisposition to DILI is still a subject of

Table 1. RUCAM score.

Type of injury	Mixed liver injury	Score
Time to onset		
• From the beginning of drug use	<90 days	+2
Change in ALP (or total bilirubin) between peak and stopping the drug	Persistence or increase or no information	0
Risk Factors:		
1. Alcohol or Pregnancy	1. No	0
2. Age ≥55 years	2. Yes	+1
Concomitant drug use	None	0
Exclusion of other causes of liver disease	The 6 causes of Group I ruled out	+1
Prior information on the hepatotoxicity	Reaction published but unlabeled	+1
Response to re-administration	Not done	0
Total score	Possible	5

debate. In general, enzyme activity tends to decrease as the severity of liver disease progresses. As a result, CYP activity can either be increased (rarely), remain unaltered, or more commonly, be reduced or significantly impaired depending on the extent of liver dysfunction.[32] Emerging evidence suggests that non-alcoholic fatty liver disease (NAFLD) may elevate the risk or severity of DILI.[33,34] The combination of these factors may have contributed to the development of acute liver failure in our patient.

In clinical practice, determining drug-induced hepatotoxicity remains challenging due to the lack of reliable markers.[14] The Roussel Uclaf Causality Assessment Method (RUCAM) is used for evaluating the likelihood of drug-induced liver injury due to a particular medication.[35] In our case, the RUCAM score was 5 (Table 1), which correlates to "possible". The timing of turmeric supplement use concerning the onset of liver injury was compatible. Moreover, the patient underwent extensive workup to rule out other causes of abnormal liver function, as well as a biopsy consistent with drug-induced liver injury.

4. Conclusion

Supplements containing turmeric have the potential to cause liver damage. Nevertheless, cases of DILI associated with turmeric supplementation have not been commonly reported in the medical literature. A careful medication history, including non-prescribed dietary supplements, remains critical to the timely identification of potential adverse reactions and therapeutic management.

Disclaimers

The abstract was presented at the MD ACP Mulholland Mohler Residents Meeting on May 11th 2023 in Baltimore, Maryland, and received an honorable mention.

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Conflicts of interest

All authors declare no conflict of interest.

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