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DRUG-INDUCED LIVER INJURY SECONDARY TO TURMERIC USE

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ABSTRACT

Turmeric is a herbal medication and spice which has been used for thousands of years in traditional Eastern medicine for its flavour, colour, and purported anti-inflammatory, antioxidant, antineoplastic and antimicrobial properties. It has recently garnered interest and popularity worldwide for these reasons. While turmeric supplements are generally safe, some reports of toxicity are emerging. Compounds like piperine are added to turmeric to enhance its bioavailability, potentially contributing to its toxicity. Here, we describe a 55-year-old woman with progressive jaundice and elevated bilirubin and liver enzymes but no evidence of acute liver failure. She was treated with N-acetyl cysteine (NAC) for 24 hours and liver function tests (LFTs) were closely monitored. As a downtrend in LFTs was noted and the patient remained asymptomatic, she was discharged with close outpatient follow-up. LFTs eventually normalized 2 months after the initial presentation. Clinicians must keep this differential in mind when evaluating acute liver injury. With our case report, we question the utility of NAC in non-acetaminophen-related liver injury and encourage further studies.

KEYWORDS

Turmeric, hepatotoxicity, supplements, drug-induced liver injury

LEARNING POINTS

- Eliciting information on recent drug or supplement use should be part of comprehensive history-taking to evaluate acute liver injury.
- Turmeric supplements which may contain piperine to enhance bioavailability are a potential source of acute liver injury.
- The role of N-acetyl cysteine in managing non-acetaminophen-related liver injury is unclear and further studies are required.

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CASE DESCRIPTION

We present the case of a 55-year-old woman with a past medical history of moderate alcohol use who presented to the emergency room with progressive jaundice, mild abdominal discomfort and elevated liver enzymes on outpatient evaluation. She had noticed dark urine and mild right upper quadrant abdominal pain for the previous 2 weeks. She was also told by multiple family members that her eyes looked yellow. Given these symptoms, she presented to her primary care physician (PCP) who noted elevated liver function tests (LFTs) and raised bilirubin and asked her to go to the emergency room. Regarding her alcohol use, she stated that she had drunk approximately two glasses of wine daily for the past 30 years, and 5 days prior to her admission, she had drunk around five drinks during Saint Patrick's Day celebrations. She initially stated she was not on any medications. However, on further questioning, she revealed that she had been taking turmeric supplements 1500 mg once daily for wrist pain, which she had started about a month prior to her presentation. On admission, vital signs were within normal limits. On examination, she was awake, alert, oriented to time, place and person, and not in any acute distress. She was noted to have scleral icterus. She did not have any stigmata of chronic liver disease including spider angiomata, ascites or hepatosplenomegaly.

Laboratory investigations (with normal laboratory values included) were notable for an alanine transaminase (ALT) of 2143 U/l (10–43 U/l), aspartate transaminase (AST) of 2025 U/l (13–41 U/l), alkaline phosphatase (ALP) of 590 U/l (5–30 U/l), gamma glutamyl transferase (GGT) of 897 U/l (5–30 U/l), total bilirubin 8.1 mg/dl (0.21.2 mg/dl), direct bilirubin 6 mg/dl (0–0.3 mg/dl) and INR 1.2 (<1.1). Ultrasound and a CT scan of the abdomen were normal. She was given a total of 19,200 mg of N-acetyl cysteine (NAC) intravenously over 24 hours on the day of admission. Over the course of the next 5 days, her ALT and AST trended down to 1,730 U/l and 1,517 U/l, respectively, with supportive therapy only. Although her jaundice persisted, she otherwise remained asymptomatic. An extensive work-up including hepatitis viruses, cytomegalovirus, smooth muscle antibody and ceruloplasmin was conducted in order to rule out any other possible causes for her presentation, but was negative. She was asked to stop taking the supplement and was discharged on day 5 of hospitalization with close outpatient monitoring. Her liver function tests normalized 2 months after her initial presentation.

DISCUSSION

Turmeric is a supplement derived from a herbaceous perennial plant, *Curcuma longa*, which belongs to the ginger family. Known for its vivid yellow colour, it has been used in traditional medicine and as a spice for thousands of years. In the last few decades, it has garnered interest in the Western world for its various culinary and medicinal uses. Turmeric supplements are generally safe, but reports of toxicity are emerging[1,2]. However, it is currently one of the most popular herbal supplements in the United States given its anti-inflammatory, antioxidant, antimicrobial and anti-cancer effects, as demonstrated in various studies[3,4]. The main compound in turmeric is curcumin, which has low bioavailability as it is poorly absorbed, rapidly metabolized, and then eliminated. Turmeric is therefore combined with other agents such as piperine, which is the major active component of black pepper, to increase bioavailability[4]. Our patient's turmeric supplement also contained piperine as an active ingredient.

While turmeric supplements have a relatively safe side-effect profile even at doses of between 4000 and 8000 mg/day, there are an increasing number of case reports demonstrating turmeric supplements can cause liver injury, especially when combined with agents such as piperine. Drug-induced liver injury (DILI), as determined by liver enzymes and serum bilirubin levels, can be divided into hepatocellular, cholestatic and mixed hepatitis based on the widely used R factor[5]. Our patient's R factor was above 5, suggesting a hepatocellular pattern of injury and consistent with other case reports of turmeric-induced liver injury. The Roussel Uclaf Causality Assessment Method (RUCAM) score for this patient[6] was 9, suggesting that turmeric was very likely the cause of the hepatotoxicity. Despite her significant alcohol use, the fact that her AST to ALT ratio was less than 1 and liver enzymes were above 1000 U/l, suggests alcohol was not the causative agent.

Interestingly, review of the literature showed that while there is a known association between alcohol consumption and acetaminophen toxicity, DILI is not associated with a greater proportion of liver-related deaths or liver transplantation in heavy drinkers compared with non-drinkers[7].

No other cases of turmeric-induced liver injury managed with NAC have been reported, making our case unique. A systematic review evaluating NAC use in non-acetaminophen-induced DILI reported improvement in transplant-free survival; however, its benefit was inconclusive in terms of overall survival. In addition, NAC showed an adequate safety profile[8]. Another study shows that there may be a survival benefit in terms of post-transplant survival, transplant-free survival, and overall survival, while the overall length of hospital stay is decreased.

With our case report, we hope to encourage clinicians to keep this aetiology in mind when they encounter acute liver enzyme elevations and to conduct a thorough medication reconciliation of both medications and supplements. We also encourage further studies examining the utility of NAC in non-acetaminophen DILI.

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