CASE REPORT

Acute liver injury following short-term use of the herbal supplement kratom

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ABSTRACT

Kratom, a tropical plant and dietary supplement with dose-dependent effects, has physiologic effects similar to opioids as well as stimulant effects. Kratom, like all dietary supplements, is not regulated in the United States and its effects have raised potential and safety concerns. This article describes a patient who presented to the ED with jaundice and acute liver injury, which after a thorough exclusion of alternative causes was attributed to kratom use.

Keywords: kratom, liver injury, hepatotoxicity, hyperbilirubinemia, herbal supplement, *Mitragyna*

CASE

A 30-year-old man presented to the ED with new-onset jaundice and complaints of abdominal pain, nausea, and dark-colored urine, which occurred progressively over the past week.

History The patient reported that 7 days ago, he had transient nausea associated with one episode of nonbilious emesis and two episodes of loose stools. Five days ago, the patient noted dark-colored urine and bilateral flank discomfort. Three days ago, he reported reduced appetite, transient epigastric abdominal pain, and light-brown stool. One day before he presented to the ED, a family member noticed yellowing of the patient's skin and eyes, which prompted him to seek medical attention.

He denied fever, chills, unexplained weight loss, pruritus, or muscle aches. His past medical history was only significant for hyperlipidemia, for which he did not take any medications. He denied any personal or family history of liver disease. Three months ago, the patient traveled to Japan on a business trip where he frequently ate sushi, but he denied any gastrointestinal illness. The patient denied recreational drug use and reported drinking two to three drinks twice monthly. Upon further questioning, the patient admitted that 2 weeks ago he began taking kratom supplements two to three times per week to treat the various aches and pains associated with practicing jiu-jitsu.

Physical examination The patient's vital signs were BP, 143/88 mm Hg; heart rate, 68 beats/minute; respirations, 16; and oral temperature, 98° F (36.7° C). The patient was alert and in no acute distress. His skin was jaundiced. Bilateral scleral icterus was noted as well as a uniformly yellow discoloration of the soft palate. The patient's abdomen was soft, nondistended, and nontender to palpation. Murphy sign was negative. No hepatomegaly, splenomegaly, spider angioma, palmary erythema, or asterixis were noted.

Diagnostic testing Samples for a complete blood cell count with differential and serum chemistries were obtained; results of both tests were within normal limits. Liver function tests revealed ALT, 1,057 U/L (normal range, less than 35 U/L); AST, 332 U/L (normal range, less than 35 U/L); total bilirubin, 6.7 mg/dL (normal range, 0.3 to 1 mg/dL); direct bilirubin, 5.1 mg/dL (normal range, 0.1 to 0.3 mg/dL); and alkaline phosphatase, 488 U/L (normal range, 30 to 120 U/L). His international normalized ratio (INR) was slightly elevated at 1.2 (normal range, less than 1.1). Urinalysis was positive for bilirubin.

The patient's initial liver function tests revealed acute liver injury with conjugated hyperbilirubinemia, suggesting cholestatic hepatitis. Additional serologic workup and

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Key points

- Though it is not FDA-approved for any medical use, kratom is becoming increasingly popular in the United States; consumers cite use of kratom for treating pain, anxiety, depression, and opioid withdrawal.
- Use is associated with the development of acute liver injury. Additional risks include *Salmonella* infection, heavy metal exposure, death, respiratory depression, and potential for addiction because of kratom's potent opioid properties.
- Consider supplement use when evaluating patients presenting with acute liver injury.

diagnostic imaging were ordered to further elucidate the cause of injury. A hepatitis panel was negative, as were tests for infectious and autoimmune hepatitis. An abdominal ultrasound was performed and revealed no evidence of acute cholecystitis, choledocholithiasis, or intra- or extrahepatic bile duct dilation.

Management The patient was prescribed ondansetron oral disintegrating tablets for symptomatic relief of nausea. Given the severity of liver injury with an unclear cause, gastroenterology was consulted. Because the patient's workup for infectious hepatitis was negative and his coagulation studies were not markedly abnormal, gastroenterology advised that the patient could be discharged with close follow-up. He was discharged with instructions to discontinue the kratom supplements and follow up with outpatient gastroenterology in 1 to 2 days.

OUTCOME

The patient was followed at weekly office visits for the next month; serial liver function tests were performed. Three weeks after discontinuation of the kratom supplements, the patient's jaundice fully resolved and liver function tests normalized. Because the patient's condition was self-limiting and more common causes of acute liver injury were ruled out, the liver damage and conjugated hyperbilirubinemia were deemed secondary to kratom use.

DISCUSSION

Kratom or *Mitragyna* is a tropical plant found in Southeast Asia that has unique pharmacologic properties and has been used as a dietary supplement. Typically, leaves are used to prepare a tea or decoction or ground into a powder and consumed. The use of kratom is common in Southeast Asia and has extended for several hundred years. The prevalence of kratom use is now increasing in other regions of the world, including Europe and the United States. Although the FDA has not approved kratom for any medical use, kratom consumers generally use it for its opioid-like or stimulant effects, including increased energy and productivity during physical labor, analgesic properties, treatment of diarrhea, and enhancement of sexual performance.[1,2] Kratom use in the United States has risen in the past decade because of its status as a legal supplement and availability for purchase online.[3] Users of kratom in the United States cite a variety of reasons for its consumption, including support for symptoms of pain, anxiety, depression, and even opioid withdrawal.[4]

The principal active ingredient responsible for the psychoactive properties of kratom is an alkaloid compound called mitragynine.[5] The psychotropic effects observed with kratom ingestion are believed to be dose-dependent. When taken at lower doses (1 to 5 g), kratom produces stimulant-like effects such as increased alertness and physical endurance.[1,4,6] Paradoxically, ingesting higher doses of kratom (5 to 15 g) produces opioid effects such as analgesia, sedation, and euphoria because mitragynine agonizes mu-opioid receptors in the central nervous system (CNS).[4,6] Because kratom can be abused and lead to dependence, it has been outlawed in several East Asian countries.[4] In addition, because of the recent rise in kratom use in the United States and its potential for abuse, the DEA has recently listed kratom as a drug and chemical of concern and there may be state regulations or prohibitions against the possession and use of this substance, even though it is not federally listed as a controlled substance.[1]

Case studies describe a wide array of organ system injury and damage related to kratom use, including kidney injury, cardiotoxicity, thyroid injury, lung injury and acute respiratory distress, neonatal abstinence syndrome, and liver injury. Hepatic injury, which is among the most common forms of injury detailed in case reports, typically presents with a pattern of cholestatic hepatitis similar to other forms

> Mitragynine, the chief alkaloid compound of kratom, is extensively metabolized in the liver.

or herb- or drug-induced liver injury. This includes transaminitis (levels above 100 units/L are common) with elevations in alkaline phosphatase (more than 200 units/L) and total bilirubin (more than 1.2 mg/dL). Kratom toxicity has resulted in death, according to the CDC, which reported more than 150 deaths in the United States linked to the supplement between 2016 and 2017.[7]

A 25-year-old man developed cholestatic liver injury (total bilirubin of 30.9 mg/dL and direct bilirubin of 28.6 mg/dL) following the ingestion of powdered kratom for 2 weeks.[8] A 70-year-old man was found to have severe cholestasis with a total bilirubin of 41 mg/dL 3 weeks after consuming kratom supplements for 4 days.[9] In both cases, an extensive evaluation for an alternative cause of acute

liver injury and conjugated hyperbilirubinemia was unremarkable. Although this patient had a similar set of symptoms and time course to the two cases reported above, he had a more profound hepatocellular injury, as evidenced by markedly elevated transaminases, and relatively mild hyperbilirubinemia.

Findings on liver biopsy following short-term kratom use include bile precipitations in hepatocytes, lymphocytic inflammation of bile ducts and canalicular cholestasis, and a constellation of findings consistent with acute cholestatic liver injury.[10] In addition, mitragynine, the chief alkaloid compound of kratom, is extensively metabolized in the liver via phase I and II reactions, posing another potential mechanism for its hepatotoxicity.[11]

The risks of kratom use extend beyond acute liver injury:

- *Respiratory depression*. Because of its potent mu-opioid receptor agonism comparable to that of prescription strength morphine derivatives, high doses of kratom alone or in combination with other CNS depressants can lead to potentially fatal respiratory depression.[4,12]
- *Abuse*. Because of its opioid properties, kratom has the potential for abuse, dependence, and withdrawal.[12]
- *Contamination*. Recently, the FDA analyzed more than 30 samples of kratom products and discovered unsafe levels of heavy metals such as lead and nickel, raising concerns for long-term kidney damage, anemia, and certain cancers.[13] Dozens of different kratom-containing products have been found to be contaminated with various strains of *Salmonella*, linking them to outbreaks in multiple states.[14] In April 2018, the FDA issued a warning about kratom after it was linked to 44 deaths, and in 2019, a separate report from the CDC directly linked kratom to 91 deaths.[7,12]

No standardized diagnostic test exists for confirming kratom exposure, although one case report describes the use of both a serum and urine assay for the detection of mitragynine.[8] Serum liver function tests in kratom-associated liver injury typically reveal conjugated hyperbilirubinemia, moderate elevations in alkaline phosphatase, and mild elevation of transaminases.[8-10,15] Liver biopsy typically is not pursued in the initial evaluation of drug-induced liver injury unless it is needed to rule out a competing diagnosis, such as autoimmune hepatitis.

Data on the management of kratom-associated liver injury are limited. However, current recommendations from the American College of Gastroenterology (ACG) on the management of drug-induced liver injury include prompt discontinuation of the suspected agent and serial liver function testing to monitor for resolution of acute liver injury.[16]

CONCLUSION

Kratom supplements are associated with acute hepatitis with a predominantly hepatocellular pattern of liver injury. Given the increasing popularity and rising use of kratom in the United States over the past decade, clinicians must be aware of the numerous health risks associated with this dietary supplement and should routinely ask about supplement use when evaluating patients presenting with acute liver injury. **JAAPA**

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