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ABOUT COVER

Editorial board member of *World Journal of Hepatology*, Dr. Fernando Oscar Bessone is Professor of Gastroenterology and Chief of the Gastroenterology and Hepatology Department at the Hospital Provincial del Centenario, University of Rosario School of Medicine (Brazil). Dr. Bessone completed postgraduate training in Clinical Hepatology, Liver Pathology (Hospital de Clinicas, San Pablo, Brazil), Pediatric Hepatology (Hospital da Criança, San Pablo, Brazil), and Liver Transplantation and Clinical Hepatology (Hospital Clinic y Provincial de Barcelona, Spain). He has served as Principal Investigator or Co-Investigator in more than 50 clinical trials, and is currently the Coordinator of the Latin American Registry of Hepatotoxicity. He authored more than 70 articles, 30 book chapters, and more than 140 papers presented at scientific meetings. In addition, he serves as an editorial board member for several international hepatology-related journals. (L-Editor: Filipodia)

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The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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Kratom induced severe cholestatic liver injury histologically mimicking primary biliary cholangitis: A case report

Darshan Gandhi, Kriti Ahuja, Alexis Quade, Kenneth P Batts, Love Patel

ORCID number: Darshan Gandhi 0000-0002-7079-450X; Kriti Ahuja 0000-0001-6878-919X; Alexis Quade 0000-0003-0394-8967; Kenneth P. Batts 0000-0002-2963-3843; Love Patel 0000-0002-6271-6376.

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Darshan Gandhi, Department of Radiology, Northwestern Memorial Hospital, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, United States

Kriti Ahuja, Department of Internal Medicine, Maulana Azad Medical College, New Delhi 110002, Delhi, India

Alexis Quade, Internal Medicine-Pediatrics, University of California-San Diego and Rady Children's Hospital San Diego, San Diego, CA 92103, United States

Kenneth P Batts, Department of Pathology, Abbott Northwestern Hospital, Allina Health, Minneapolis, MN 55407, United States

Love Patel, Division of Hospital Medicine, Abbott Northwestern Hospital, Allina Health, Minneapolis, MN 55407, United States

Corresponding author: Darshan Gandhi, MD, Academic Fellow, Doctor, Department of Radiology, Northwestern Memorial Hospital, Northwestern University Feinberg School of Medicine, 676 N St. Clair St, Suite 800, Chicago, IL 60611, United States. darshangandhi7@gmail.com

Abstract

BACKGROUND

Kratom is a psychoactive substance that is isolated from the plant *Mitragyna speciosa*. The leaves can be chewed fresh or dried, smoked, or infused similar to herbal teas. The plant leaves have been used by natives of Southeast Asia for centuries. The substance has been used for its stimulant activity at low doses, and as an opium substitute at higher doses due to a morphine like effect.

CASE SUMMARY

A 37-year-old female with a history of depression and obesity (body mass index: 32) presented to emergency room with a week-long history of nausea, decreased appetite, fatigue, and two days of jaundice. On admission bilirubin was markedly elevated. Her condition was thought to be due to consumption of Kratom 2 wk before onset of symptoms. Liver biopsy showed changes mimicking primary biliary cholangitis. Patient's symptoms and jaundice improved quickly.

CONCLUSION

The use of Kratom has been on the rise in recent years across the United States and Europe. Several case reports have associated adverse health impact of

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Kratom-containing products including death due to its ability to alter levels of consciousness. Only a few case reports have highlighted the hepatotoxic effects of Kratom. Even fewer reports exist describing the detailed histopathological changes.

Key Words: Case report; Kratom; Cholestasis; Liver injury; *Mitragyna speciosa*; Cholangitis; Substance induced injury

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Core Tip: Kratom induced liver injury is an important differential diagnosis for physicians to consider in any patient presenting with acute liver injury. As observed in our patient, this manifestation of Kratom consumption may occur even at low doses. Further, this case report demonstrates that a thorough history is essential for an accurate and timely diagnosis. Patients may consider dietary and herb supplements to be natural and risk-free products, not realizing the potential for harm. In addition to asking their patients about consumption of any supplements, it is imperative that physicians update themselves so as to be able to discuss the benefits and risks, and counsel their patients effectively. Identifying use of supplements helps in early diagnosis and treatment, while also preventing future harm. From the pathology perspective, biliary changes associated with Kratom injury can mimic primary biliary cholangitis.

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INTRODUCTION

Acute liver failure is a severe condition which may rapidly become fatal^[1]. In the United States, a significant number of these cases occur due to drug-induced liver injury^[2]. Apart from prescribed medications, consumption of herbal and dietary supplements also plays an important role in causing liver injury^[2]. We present here a case of a 37-year-old female, with drug induced liver injury mimicking as antimitochondrial antibody (AMA) negative primary biliary cholangitis (PBC), secondary to consumption of an herbal supplement, Kratom. Derived from the leaves of *Mitragyna speciosa*, a plant found in Southeast Asia and Africa, this supplement is used for its stimulant properties, as a substitute for opioids, and to help opioid withdrawal symptoms^[3]. People in the United States report using this supplement predominantly for pain relief, and also report increased levels of energy and focus with consumption^[4]. Our patient learned of this herbal supplement from a friend and reported consuming it in order to boost her energy levels. Although uncommon, this herbal supplement is associated with the risk of hepatotoxicity, making it imperative for physicians to be aware of its harmful effects and caution their patients against its use^[4].

CASE PRESENTATION

Chief complaints

A 37-year-old female with a history of depression and obesity (body mass index: 32) presented to emergency room with a week-long history of nausea, decreased appetite, fatigue, and two days of jaundice.

History of present illness

Four days prior to admission, she noticed that her stools were becoming tanner and

eventually turned white. She also reported that her urine was dark. Two days prior to admission the patient noticed jaundice and scleral icterus which prompted her to seek treatment. Her only home medication was venlafaxine, which she had been taking for several years. She has no history of alcohol abuse.

On further questioning about new medications or supplement use, the patient reported using an herbal supplement containing Kratom two weeks prior to the onset of her symptoms. She used the supplement for the first time in her life. Encouraged by a friend to use the supplement to “boost energy levels,” she believed it was safe because it was “all natural”. She consumed approximately three grams in total over the course of three days in the form of powder (which she dissolved in water) and tablets. During her hospitalization, the patient’s liver enzymes continued to rise. On day 3 of her hospitalization, a liver biopsy was performed.

History of past illness

History of depression and obesity.

Physical examination

Unremarkable except jaundice.

Laboratory examinations

On admission, the patient had markedly elevated liver enzymes (Table 1). Other basic laboratory findings including blood count, basic metabolic panel, coagulation panel, serum thyroid stimulating hormone and antinuclear antibody were within normal range. Viral and autoimmune hepatitis studies were normal. Ceruloplasmin level was also normal. AMA was negative.

Imaging examinations

An abdominal ultrasound showed diffuse increased echogenicity of the liver with normal liver size and contour suggests diffuse hepatic steatosis (Figure 1). No intrahepatic or common biliary duct dilation or gall stones seen. An abdominal computed tomography scan showed similar findings. Magnetic resonance cholangiopancreatography did not demonstrate any further abnormalities.

FINAL DIAGNOSIS

Kratom induced severe liver injury histologically mimicking PBC.

TREATMENT

The patient was started on prednisone 40 mg daily. Advised to avoid any new medications or over the counter products with the potential risk of liver injury till her liver enzymes normalized.

OUTCOME AND FOLLOW-UP

The patient was discharged on day 5 of hospitalization and follow up was arranged with gastroenterology clinic. The patient had liver enzymes checked six days after discharge; her symptoms and liver enzymes showed marked improvement. Steroids were stopped. Patient was lost to further lab follow up with gastroenterology clinic but reported feeling back to her normal on follow up phone call 2-wk post hospitalization.

DISCUSSION

The herbal supplement Kratom is a psychoactive substance derived from the leaves of *Mitragyna speciosa*, a plant native to Southeast Asia^[3]. Its leaves are used for a variety of purposes, such as pain relief, enhancing energy levels, substituting opioids, managing opioid withdrawal^[3,4]. The psychoactive compounds of Kratom, mitragynine, and 7-hydroxymitragynine may also result in altered consciousness, particularly at high doses of consumption^[3]. As a result, Kratom is a controlled drug in several countries

Table 1 Patient's liver function labs from the day after admission until the day of hospital discharge

| | HD1 | HD2 | HD3 | HD4 | HD5 | Six days post- discharge | Normal values |
|----------------------------|------|------|------|------|------|--------------------------|---------------|
| Total bilirubin (mg/dL) | 10.3 | 12.0 | 14.5 | 17.2 | 19.5 | 5.7 | < 1.0 |
| Alkaline phosphatase (U/L) | 672 | 677 | 744 | 817 | 839 | 507 | 50-160 |
| ALT (U/L) | 578 | 585 | 600 | 608 | 591 | 323 | 0-30 |
| AST (U/L) | 455 | 461 | 437 | 401 | 385 | 101 | 0-40 |

HD: Hospital day; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

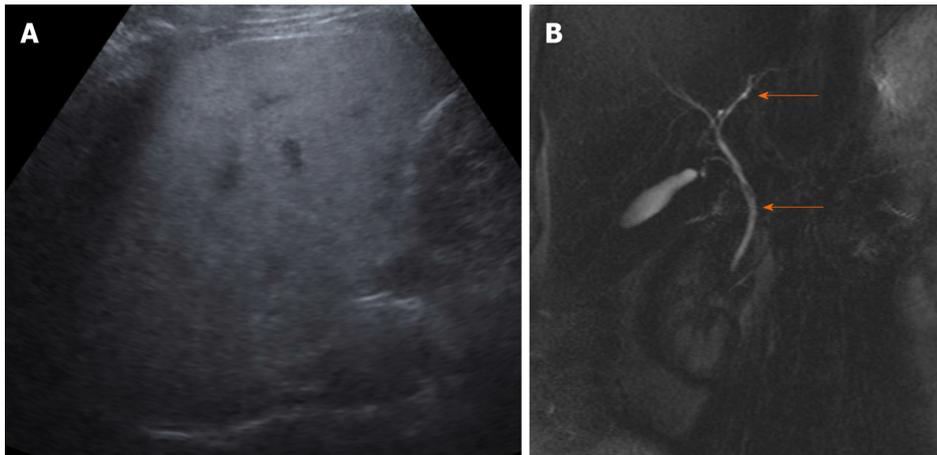


Figure 1 The abdominal ultrasound. A: Diffuse fatty infiltration of liver; B: Normal common bile duct and intrahepatic biliary ducts (orange arrows) in magnetic resonance cholangiopancreatography 3D image.

and illegal in several others^[5]. The Drug Enforcement Administration of the United States considers it a Drug and Chemical of Concern^[6]. While Kratom products are legal in most parts of the United States, a few states and cities have banned them^[4]. With concerns regarding its safety, the Food and Drug Administration warns consumers against the use of these products^[4,7].

Further, studies have shown that patients reporting Kratom use may present with confusion, lethargy, irritability, agitation, nausea and vomiting, tachycardia, hypertension or in severe cases, bradycardia, seizures, increased bilirubin, renal failure and even coma^[4]. Further, Kratom is also reported to exert effects similar to opioids, such as sedation, hypnosis, nausea, stupor and respiratory depression^[3,4,8]. In addition to this, the Food and Drug Administration has recalled Kratom supplements due to contamination with *Salmonella*^[9].

Although Kratom induced liver injury is described, reports with detailed description of histopathological changes are rare which are mentioned below in **Table 2**. Rapid clinical and liver enzyme improvement supports the diagnosis of Kratom induced liver injury.

An interesting aspect of our case is the pathological features of liver injury (**Figure 2**). The zone 3 cholestasis was felt to reflect drug effect; zone 3 cholestasis is a common finding in cholestatic drug reactions but not a feature of early stage PBC. The lymphocytic cholangitis, a typical feature of PBC and unusual medication-injury finding, raised initial concern for underlying early stage PBC. This is of lesser concern given her negative antinuclear antibody and AMA status, trend toward rapid resolution of liver enzymes, and a case report by Aldyab *et al*^[10] in 2019 that reported a case of kratom toxicity with granulomatous cholangitis (another form of florid duct lesion) that mimicked PBC. This was from a 40-year-old female presenting with liver injury after Kratom use who initially perceived to have AMA-negative PBC but diagnosed with Kratom induced liver injury after rapid normalization of liver enzymes.

In the first published case report of intrahepatic cholestasis due to consumption of Kratom, the patient's laboratory results showed a peak bilirubin of 29.3 mg/dL with prolonged elimination based on known half-life of the drug and analysis of urine

Table 2 Kratom-induced hepatotoxicity with review of literature in patients with liver biopsy

| Ref. | Age, sex | Clinical findings | Form, amount, duration of Kratom consumed | Peak bilirubin (mg/dL) | Disease pattern | Radiological findings | Histological findings |
|--|----------|--|--|---|---|---|---|
| Kapp <i>et al</i> ^[11] | 25, M | Abdominal pain, brown urine, jaundice, pruritus | Powder, 1 to 2 teaspoon twice a day and increased to 4-6 teaspoon over 2 wk (1 teaspoon approximately 2-3 g) | Direct bilirubin 29.3 | Cholestatic (increased bilirubin, AST, ALT, ALP) | USG, CT-hepatic steatosis | Cholestatic injury, no hepatocellular damage, canalicular cholestasis |
| Drago <i>et al</i> ^[14] | 23, M | Jaundice, pale stool, brown urine for 4 d | Powder, 85 g total over 6 wk | Direct bilirubin 5.8 | Cholestatic (increased bilirubin, AST, ALT, ALP) | USG, CT-normal | Cholestatic liver injury |
| Bernier <i>et al</i> ^[15] | 41, F | Jaundice, diarrhea, pruritus | Form not available, 1 teaspoon twice daily for 1 wk | Direct bilirubin 15 | Cholestatic (increased bilirubin, AST, ALT, ALP) | - | Intralobular bile duct destruction with cholestatic overload |
| Shah <i>et al</i> ^[16] | 30, F | Abdominal pain, jaundice, dark urine, pruritus | Tea containing Kratom, dose not available | Direct bilirubin 18 | Cholestatic (increased bilirubin, AST, ALT, ALP) | MRI-normal, ERCP-no bile duct obstruction | Intrahepatic cholestasis |
| Rivero <i>et al</i> ^[13] | 38, M | Dark urine, light stools, fever | Not available | Total bilirubin 5.6 | Cholestatic (increased bilirubin, AST, ALT, ALP) | USG-normal | Acute cholestatic injury, mild bile duct injury, portal inflammation |
| Mackenzie <i>et al</i> ^[17] and De Francesco <i>et al</i> ^[18] | 27, M | Vomiting, epigastric pain, diarrhea with associated heavy alcohol intake | Powder, 3-4 teaspoon multiple times weekly for several wk | Total bilirubin 11.2 | Cholestatic (increased bilirubin, AST, ALT, ALP) | - | Widespread hepatocellular necrosis with extracellular cholestasis |
| Fernandes <i>et al</i> ^[12] | 52, M | Mild fatigue, jaundice | Crushed leaves with water, 1 teaspoon (approximately 1.5 g) once or twice a day for 2 mo | Total bilirubin 28.9 | Cholestatic (increased bilirubin, ALP; slightly increased AST, ALT) | MRI - normal | Canalicular cholestasis, bile duct injury, hepatic lobule injury, mixed inflammation in portal tracts |
| Aldyab <i>et al</i> ^[10] | 40, F | Abdominal pain, fever | Form not available, once a week for 1 mo | Total bilirubin 5.1 | Mixed cholestatic and hepatocellular (increased bilirubin, AST, ALT, ALP) | CT, MRCP-mild, nonspecific periportal edema | Granulomatous duct injury |
| Pronesti <i>et al</i> ^[19] | 30, M | Dark urine and pale stool for 1 wk, scleral icterus for 1 d | Powder with water, for 4-6 wk | Total bilirubin 5.7, direct bilirubin 4.5 | Cholestatic (increased bilirubin, AST, ALT, ALP) | USG-coarse hepatic echotexture | Hepatocellular and canalicular cholestasis with inflammation and focal prominent eosinophils. No fibrosis |
| LiverTox case 6972 ^[20] | 25, M | Abdominal pain, fever, jaundice, dark urine, pruritus | Powder, for 23 d | Total bilirubin 22.4 | Mixed Hepatocellular and cholestatic (increased bilirubin, AST, ALT, ALP) | USG, CT-gall bladder wall thickening with increased perihepatic lymph nodes | Cholestatic injury with mild necrosis and inflammation |

M: Male; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; USG: Ultrasonography; CT: Computed tomography; F: Female; MRI: Magnetic resonance imaging; ERCP: Endoscopic retrograde cholangiopancreatography; MRCP: Magnetic resonance cholangiopancreatography.

samples^[11]. It was speculated that this could be due to the patient's underlying steatohepatitis^[11]. Similarly, our patient also had steatohepatitis observed on imaging and pathology, which could explain why even the relatively low doses of Kratom used by our patient compared to other cases discussed in the literature led to such profound liver injury.

As Kratom use appears to be on the rise in the United States, physicians need to be aware of its potential for adverse effects^[4,9]. This case highlights how even small

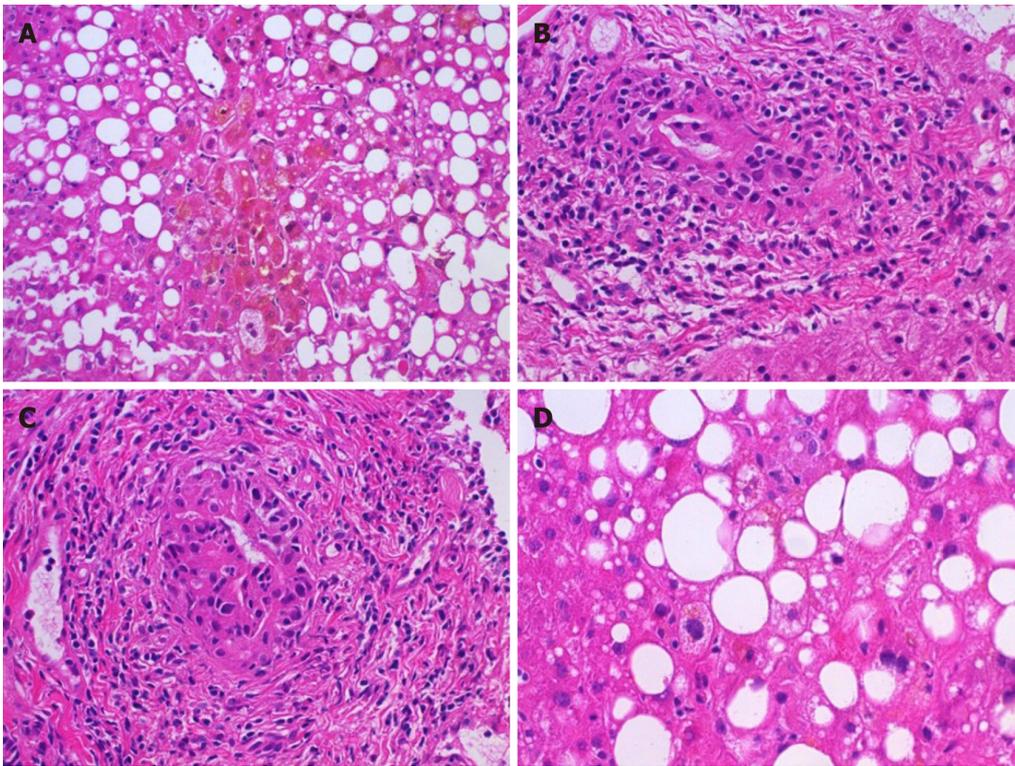


Figure 2 Histopathological findings. A: Centrilobular areas showed well defined cholestasis; B and C: Portal tracts showed moderate chronic inflammation and brisk lymphocytic-predominant bile duct injury; D: Background liver showed steatohepatitis which was felt to most likely be due to underlying obesity-related non-alcoholic fatty liver disease.

amounts of the supplement can be hepatotoxic. Physicians need to be able to discuss safety concerns of over-the-counter supplements with their patients. Moreover, the rising use of supplements and recreational substances can pose diagnostic challenges for clinicians when their use is not reported. Medical providers always need to consider the use of supplements when patients present with possible drug-induced liver injury.

CONCLUSION

Kratom induced liver injury is an important differential diagnosis for physicians to consider in any patient presenting with acute liver injury. As observed in our patient, this manifestation of Kratom consumption may occur even at low doses. Further, this case report demonstrates that a thorough history is essential for an accurate and timely diagnosis. Patients may consider dietary and herb supplements to be natural and risk-free products, not realizing the potential for harm. In addition to asking their patients about the consumption of any supplements, it is imperative that physicians update themselves so as to be able to discuss the benefits and risks and counsel their patients effectively. Identifying use of supplements helps in early diagnosis and treatment, while also preventing future harm. From the pathology perspective, biliary changes associated with Kratom injury can mimic PBC.

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