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CASE REPORT | LIVER

Multiorgan Dysfunction Related to Kratom Ingestion

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ABSTRACT

Consumption of herbal supplements has been linked to multiorgan toxicities. Kratom is an herbal extract that has gained popularity for its analgesic and psychotropic properties. Several cases of kratom-induced liver injury have been reported, but data on multiorgan involvement remain scarce. We present the case of a 37-year-old woman who developed a mixed hepatocellular and cholestatic pattern of acute liver injury, acute kidney injury, and pancolitis after prolonged use of kratom-containing herbal supplements.

INTRODUCTION

Kratom, or *biak-biak*, is derived from *Mitragyna speciosa*, a tree indigenous to Southeast Asia. Kratom as a supplement has been used for fatigue, pain, mood, and euphoria because it interacts with the serotonergic (5-HT) and μ-opioid receptors to produce favorable psychotropic and antinociceptive effects, respectively.[1] As a result of widespread availability and lack of regulation, the misuse of kratom is on the rise. The drug enforcement administration has warned consumers about the potential side effects of kratom, including hepatotoxicity and withdrawal, but the spectrum of kratom toxicity in humans is not well described.[1,2] We report an atypical presentation of kratom-induced acute liver injury (ALI) associated with simultaneous renal failure and pancolitis. To the best of our knowledge, this is the first description of multiorgan dysfunction in the setting of prolonged kratom ingestion.

CASE REPORT

A 37-year-old woman with a history of hypertension, attention-deficit hypersensitivity disorder, and chronic back pain presented with a 2-day history of abdominal pain, nausea, vomiting, and watery diarrhea. She denied any personal or family history of liver disease. She denied the use of alcohol, tobacco, and illicit substances. She endorsed the ingestion of 3 capsules of kratom-containing herbal supplements daily for a year, in addition to amphetamine/dextroamphetamine for attention-deficit hypersensitivity disorder. On examination, vital signs were within normal ranges, and her mental status examination was also normal. Initial laboratory tests were notable for hemoglobin 9.4 g/dL, blood urea nitrogen 99 mg/dL, creatinine 7.8 mg/dL, alkaline phosphatase 334 U/L, aspartate aminotransferase 564 U/L, alanine aminotransferase 565 U/L, total bilirubin (TB) 4.1 mg/dL, direct bilirubin 3.6 mg/dL, and international nationalized ratio 1.0. The patient was admitted for further evaluation. A computed tomography scan of the abdomen subsequently demonstrated pancolitis. This finding was confirmed by colonoscopy, which revealed diffusely erythematous and edematous mucosa throughout the colon, with deep serpiginous ulcers in the rectum and descending colon. She was treated with intravenous antibiotics and corticosteroids empirically for panulcerative colitis. Within the first week of hospitalization, the patient developed progressive oliguric acute kidney injury; her evaluation, including urine analysis, suggested acute tubular necrosis with evidence of muddy brown casts and an absence of eosinophils. She eventually required the initiation of renal replacement therapy for anuria.

Over the course of her hospitalization, the patient developed progressive jaundice. On day 10 of admission, her liver biochemistries were as follows: alkaline phosphatase 648 U/L, aspartate aminotransferase 310 U/L, alanine aminotransferase 230 U/L, TB 11.3 mg/dL, direct bilirubin 7.8 mg/dL, and international nationalized ratio 1.6. An magnetic resonance cholangiopancreatography was notable for

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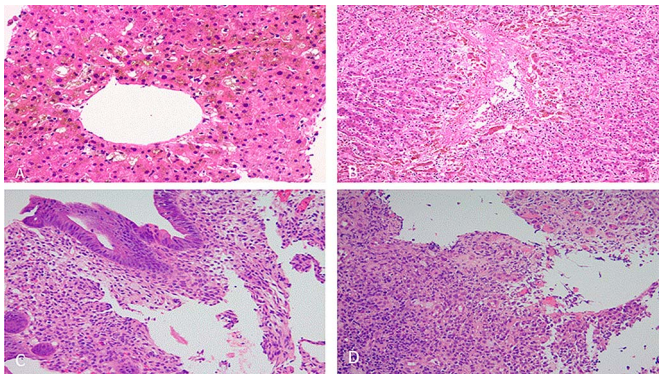

Figure 1. (A) Liver: canalicular cholestasis surrounding the central veins with associated bile duct injury. (B) Liver: zone 3 cholestasis and bile duct injury with patchy hepatocyte necrosis. Hematoxylin and eosin stain. (C) Sigmoid colon: surface epithelium with reactive changes, eosinophilic cytoplasm, and disorganized epithelial cell placement. Rare neutrophils are seen with the underlying lamina propria devoid of the normal glandular elements. (D) Sigmoid colon: ulcerated mucosa replaced with granulation tissue (hematoxylin and eosin stain).

cholelithiasis without biliary ductal dilatation. Serologies for infectious causes of hepatitis were negative, including serologies against Epstein–Barr virus, cytomegalovirus, varicella-zoster virus, herpes simplex virus, human immunodeficiency virus, and hepatitis A, B, C, D, and E. Testing for autoimmune hepatitis was also negative, including antinuclear antibodies, anti–double-stranded DNA antibody, antiribonucleoprotein antibody, anti-Jo-1 antibody, antismooth muscle antibody, antimitochondrial antibody, and Anti-Sjögren's syndrome Type A/Anti-Sjögren's syndrome Type B antibody. Finally, testing for genetic etiologies of acute and chronic liver diseases was unrevealing. Her ceruloplasmin level was 16 mg/dL with a normal 24-hour urine copper quantification. Toxicology screening was negative for metals, cannabinoids, opioids, amphetamines, and benzodiazepines. She underwent a transjugular liver biopsy; histology revealed centrizonal cholestasis and bile duct loss, most consistent with drug-induced liver injury (Figure 1). Her cholestasis was treated with ursodiol.

Despite ongoing intravenous corticosteroid therapy, the patient continued to have fulminant diarrhea. Stool studies for *Salmonella*, *Shigella*, *Campylobacter*, *Clostridium difficile*, and *Escherichia coli* were negative. Repeat endoscopic investigation through a sigmoidoscopy noted severe necrotic and ulcerated mucosa with active inflammation in the rectum, sigmoid colon, and descending colon. Biopsies from the sigmoid colon revealed ulceration with granulation tissue. Immunohistochemical staining was negative for Epstein–Barr virus, cytomegalovirus, and adenovirus (Figure 1). Her corticosteroids were tapered in the absence of meaningful improvement in diarrhea. In the fourth week of her hospitalization, the patient developed hemodynamic instability associated with toxic colitis, which prompted an urgent subtotal colectomy with end ileostomy. Intraoperative biopsy of the colon demonstrated extensive mucosal ulceration and regenerative epithelial changes with minimal fibrosis. After 10 weeks of hospitalization, her diarrhea improved, and she progressed to discharge.

In the absence of other explanatory etiologies, the patient's long-term use of a kratom-containing herbal supplement was believed to be the likely culprit for her severe multisystem organ dysfunction. She was advised to discontinue any form of herbal supplementation and was prescribed ursodiol. Despite aggressive supportive care, her cholestatic liver injury persisted. Her TB peaked at 25.7 mg/dL with an associated Model for End-Stage Liver Disease—Sodium score of 36. Seventeen weeks after presentation, she underwent successful orthotopic liver transplantation for subacute liver failure secondary to drug-induced liver injury. Her diarrhea has resolved; however, she has not recovered her renal function and remains on dialysis for end-stage renal disease.

DISCUSSION

Recreational misuse of kratom has been gaining momentum in the United States. According to a recent report, the past-year prevalence of kratom use in the United States was 0.8%.[3] This relatively widespread consumption has been attributed partly to its increasing appeal as an alternative to opioid use and partly to its accessibility. Kratom is primarily metabolized in the liver; its analgesic effects are due to the presence of alkaloid compounds, especially mitragynine and its derivative 7-hydroxymitragynine. Studies that examine the pharmacokinetics of kratom in humans are limited; as a result, the spectrum of adverse effects is not well documented.[4,5]

Cases reporting kratom-induced ALI describe either cholestatic or mixed liver injury with a mean latency period of approximately 21 days.[6] We describe the case of a patient who presented with a mixed pattern of ALI, but uniquely, her latency period was at least 1 year. It is hypothesized that kratom inhibits the activity of certain hepatic CYP450 enzymes, which may predispose to drug–drug interactions and related toxicity, but more studies are needed to define a clear mechanism of action.[7] Although there are reports of neurological symptoms associated with concurrent kratom and amphetamine/dextroamphetamine ingestion, the pharmacodynamics are not well understood.[8] Moreover, the literature describes cases of acute kidney injury related to kratom ingestion, but none of the patients in these reports developed end stage renal disease or required long-term dialysis, as in the case of our patient.[6,9]

Finally, we report a unique case of fulminant colitis associated with kratom use and with kratom-induced ALI. The contamination of kratom products by *Salmonella* sp. has been recognized in the literature, but thorough testing for *Salmonella* in our patient was negative.[10] The syndrome of drug-induced colitis has well described; histopathological findings of drug-induced colitis are nonspecific and can be similar to ischemic colitis, which may present a diagnostic dilemma.[11] To the best of

our knowledge, this is only the second reported patient to require orthotopic liver transplantation for acute liver failure as a consequence of kratom ingestion.[12] This case highlights the potential association of severe multiorgan dysfunction related to "therapeutic misadventure" with over-the-counter herbal supplements and drugs. Without a standard regulatory mechanism for distribution and monitoring, the general public may be at continued risk of systemic toxicity related to both acute and chronic kratom ingestion.

DISCLOSURES

Author contributions: MZ Khan wrote the manuscript, reviewed the literature, and is the article guarantor. MA Saleh, M. Alkhayyat, and CC Lindenmeyer reviewed the literature and revised the manuscript for intellectual content. DE Roberts provided the images.

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