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CASE REPORTS

Ketamine-Induced Sclerosing Cholangitis Associated With Early Inflammatory Bowel Disease During Chronic Topical Ketamine Use

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Ketamine-induced sclerosing cholangitis has been described with chronic intranasal and intravenous use. Our case follows chronic topical use for peripheral neuropathy. It is also uniquely associated with early inflammatory bowel disease, a known complication of primary sclerosing cholangitis.

Keywords: Ketamine; Primary Sclerosing Cholangitis; Inflammatory Bowel Disease; Drug-Induced Liver Injury

Introduction

Ketamine, a phencyclidine derivative, is a safe, water- and lipid-soluble, intravenous general anesthetic that has been in clinical use since the 1970s.[1] The drug is metabolized in the liver to an active metabolite norketamine by microsomal cytochrome enzymes 2 and excreted in urine and bile.

Ketamine-associated uropathy has been described in ketamine abusers.[3] It is characterized by urinary bladder dysfunction (recurrent episodes of nocturia, dysuria, increased urinary frequency and hematuria, inflammation, cystitis, and morphological changes in the bladder wall).[4,5] The mechanism appears to be direct toxicity by ketamine or its metabolites on the urinary epithelium. In one rare case of a urachal cyst, differential damage to the bladder wall exposed to urine was noted, whereas the epithelium of the urachal cyst in the dome of the bladder, which was unexposed to urine was intact.[6]

Long-term recreational abuse and prolonged therapeutic ICU use have also been associated with ketamine-induced sclerosing cholangitis (KISC). The typical presentation is with recurrent epigastric pain and elevated serum cholestatic enzymes alkaline phosphatase (ALP) and GGT. Abnormalities in MRCP and ERCP at presentation show changes consistent with sclerosing cholangiopathy.[7–10]

We report a case of KISC after prolonged topical ketamine use for peripheral neuropathy. There were also mucosal changes in the colon suggestive of early inflammatory bowel disease.

Case Report

A 38-year-old female first presented to the emergency room in September 2021 with pain in the right upper quadrant and elevated ALP. She had a history of Alport syndrome, with 2 prior renal transplants. She also had a history of chronic interstitial cystitis dating back several years.

Multiple liver chemistries documented over a three-year period, between August 2018 and March 2021, had been completely normal. Specifically, her serum ALP had consistently been less than 113 u/L.

Between April 2021 and her first presentation with RUQ pain in September 2021, there had been a slow increase in ALP from 354 u/L to 985 u/L with concomitant GGT elevation to 1060 u/L (N < 38 u/L). In the ER, ultrasound showed multiple small and large stones in the gallbladder. A successful laparoscopic cholecystectomy was performed in September 2021. Histology showed chronic cholecystitis and cholelithiasis. It was negative for malignancy. She made a good recovery from this episode.

However, between September 2021 and November 2022, she had multiple hospital admissions for epigastric pain with nausea and vomiting. Serum bilirubin remained normal. Serological workups, including ANA, AMA, and IgG4 were unrevealing, as were routine viral tests. EBV and CMV infections were ruled out.

She admitted to regular topical use of compounded ketamine and lidocaine lotion over several months for peripheral neuropathy.

A liver biopsy was performed in April 2022. It showed expansion of portal tracts with edema, bile ductular proliferation, neutrophilic inflammation, and focal bile duct injury with focal periportal fibrosis (Figure 1). Immunohistochemical stain for CMV was negative.

Abbreviations used in this paper: **AMA, antimitochonrial antibody; ANA, antinuclear antibody; CMV, cytomegalovirus; EBV, epstein-Barr virus; ER, emergency room; ERCP, endoscopic retrograde cholangio-pancreatography; FDA, Food and Drug Administration; GI, gastro-intestinal; HPF, high power field; ICU, intensive care unit; IgG, immunoglobulin G; MRCP, magnetic resonance cholangiopancreatography; RUQ, right upper quadrant.**

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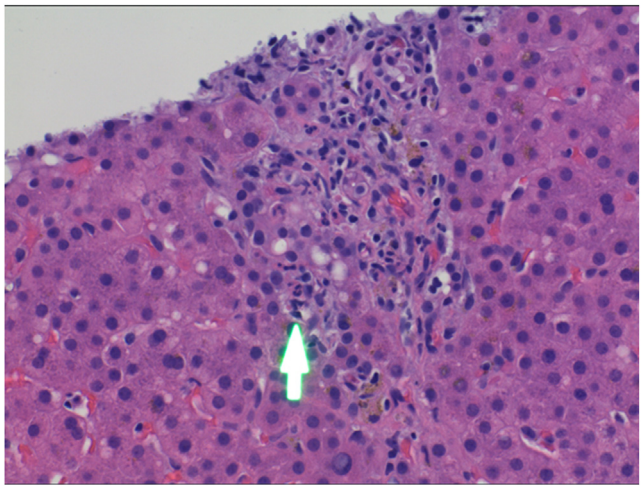

Figure 1. Liver biopsy showing expansion of portal tracts with edema, bile ductular proliferation, neutrophilic inflammation, and focal bile duct injury with focal periportal fibrosis consistent with bile duct obstruction. Immunohistochemical staining for CMV was negative.

MRCP showed abnormal peribiliary restricted diffusion with corresponding increased peribiliary T2 signal, consistent with cholangitis (Figure 2). ERCP with balloon cholangiography showed the absence of intraluminal filling defects. Peripheral ducts were pruned, suggestive of small duct sclerosing cholangitis (Figure 3).

She complained of recurrent hematochezia during one of her several hospital admissions on October 2022. A colonoscopy was performed. This noted skip lesions in the colon. Biopsies of the rectal mucosa showed focal ulceration with severe activity and fibrinopurulent exudate. The ascending colon showed focally, severely active ulcerated mucosa with increased lamina propria eosinophils (up to 75 per HPF). The differential diagnosis included infection, drug or medication effect, or early inflammatory bowel disease (Figure 4). Although she had been on chronic immunosuppressive drugs for her renal transplant for several years, she had not started any other drug therapy and GI infection had been ruled out.

She stopped ketamine in September 2022. She continued to be followed in the clinic, after discontinuation of topical ketamine. Her abdominal pain subsided and regular admission for abdominal pain stopped. Her ALP, which had peaked at 1861 u/L on October 2022 fell gradually and was last recorded at 485 u/L on August 2023.

Discussion

Our case illustrates KISC after long-term topical use. Previous cases described in the literature had followed ketamine inhalation in drug abusers or intravenous use in ICU setting. Urinary levels of ketamine are frequently positive in patients using topical ketamine [11] and severe acute central nervous system toxicity has been described in a pediatric case following topical ketamine use.[12] Thus, significant transcutaneous absorption of ketamine can occur.

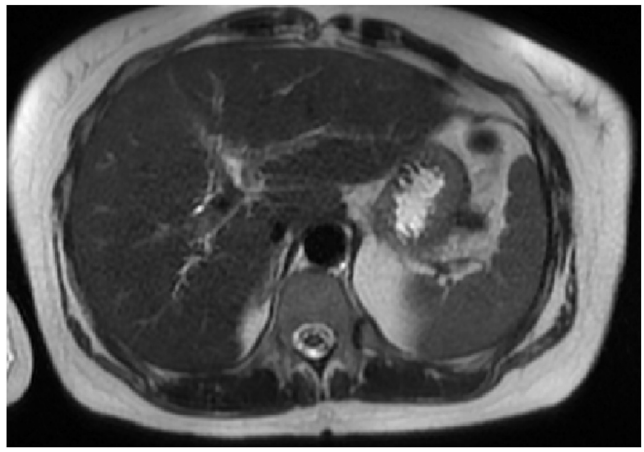

Figure 2. MRCP showing abnormal peribiliary restricted diffusion with corresponding increased T2 signal suggestive of cholangitis.

The mechanism of damage to the bladder appears to be direct toxicity by ketamine or its metabolites on the urinary epithelium. In one rare case of a urachal cyst, differential damage to the bladder wall exposed to urine was found, whereas the epithelium of the urachal cyst in the dome of the bladder that was unexposed to urine was intact.[6]

Chronic interstitial cystitis was a pre-existing condition in our patient. Therefore, it is not clear whether there was bladder involvement. However, our case appears uniquely associated with early inflammatory bowel disease. Presentation was with recurrent hematochezia. Hemoglobulin levels had been stable.

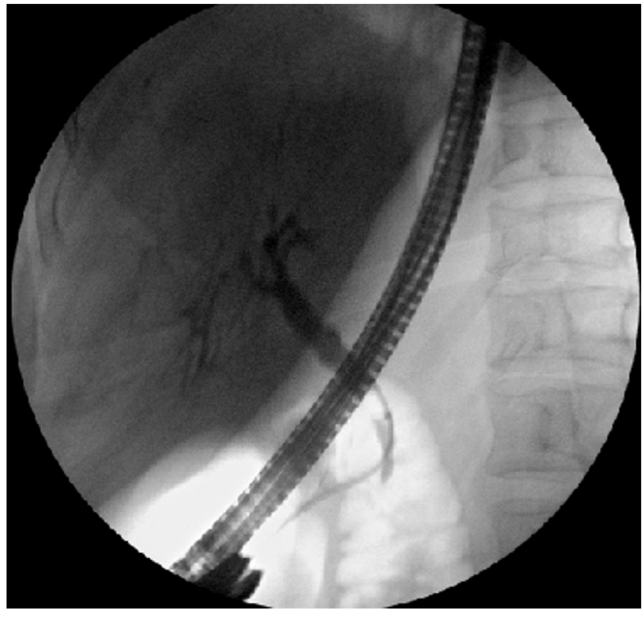

Figure 3. ERCP with balloon cholangiography shows the absence of intraluminal filling defects. The peripheral ducts are irregular and appear pruned, consistent with sclerosing cholangitis.

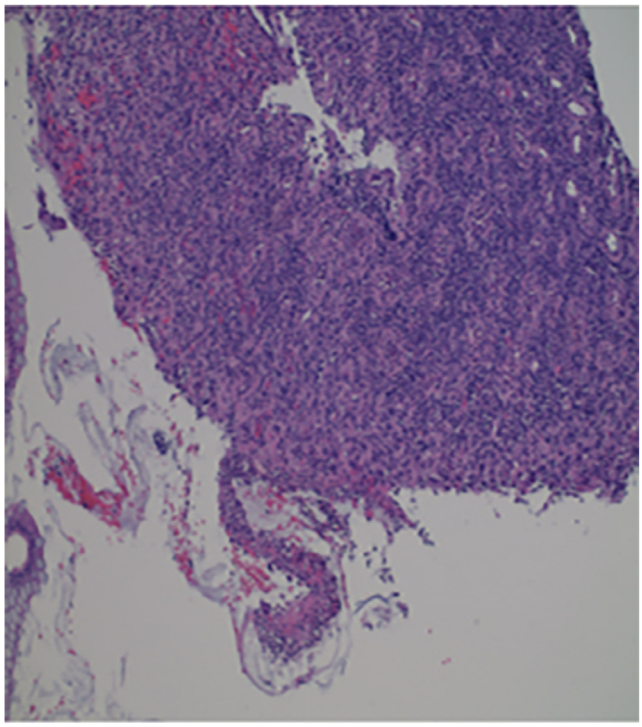

Figure 4. Colonoscopy was performed for hematochezia. Ascending colon biopsy showing severe ulceration with abundant neutrophils, lymphocytes, and scattered eosinophils. The differential diagnosis includes infection, drug or medication effect, or early inflammatory bowel disease.

Primary sclerosing cholangiopathy is clinically associated with inflammatory bowel disease.[13,14] Both diseases have been considered related to autoimmunity. However, this case raises the possibility of direct toxicity from circulating toxins, presumably originating from the liver and bile ducts and excreted via the gastrointestinal tract and urine.

There have been several developments in the use of ketamine in the treatment of psychiatric disorders, including depression and post-traumatic stress disorder.[15–18] Ketamine has a more rapid and longer lasting action compared to other available antidepressants [19] and has rapidly gained favor in the off-label chronic treatment of these conditions.

Esketamine is a formulation of ketamine approved by the FDA as a nasal spray for the treatment of treatment-resistant depression.[20] There are no available reports of KISC with this drug.

Our case suggests caution in the chronic treatment of these conditions, especially under off-label conditions, with frequent monitoring of liver function tests.

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This study did not require the approval of an institutional review board.

Reporting Guidelines:
CARE.