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Chronic Ketamine Abuse Associated with Cholestasis and Cholangitis: A Case Report

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ABSTRACT

Ketamine is an anesthetic drug that has been used in clinical settings since the 1960s. Unfortunately, this medication has been abused as a recreational drug among partygoers and youth over the last 30 years. Recently, mounting of evidence has shown the association between chronic ketamine abuse and urinary tract complications. However, not many are aware that chronic ketamine abuse may also be responsible for cholestasis and cholangitis. We report a case of urinary tract complication from chronic ketamine abuse in combination with cholestasis, cholangitis, and early liver cirrhosis related to the drug. Public awareness about ketamine abuse and its complications should be communicated. Physicians should have a high index of suspicion for ketamine abuse in someone presenting with lower urinary tract symptoms along with jaundice, abdominal pain, and abnormal liver function.

INTRODUCTION

Ketamine is an anesthetic drug that has been used in clinical settings since the 1960s. Unfortunately, this medication has been abused as a recreational drug among partygoers and youth over the last 30 years. Recently, mounting evidence has shown the association of chronic ketamine abuse with ulcerative cystitis and obstructive uropathy. However, little literature addresses the "street ketamine"-associated cholestasis and cholangitis, which may actually affect these same groups of patients. We report a chronic ketamine abuser who had suffered from cholestasis, cholangitis, and early liver cirrhosis.

CASE REPORT

A 25-year-old Chinese male electrical technician, with no known previous medical illness, presented with a 2-month history of generalized lethargy and lower urinary tract symptoms. Upon clinical examination, he looked dehydrated and lethargic. His vital signs were stable, with blood pressure of 128/70 mmHg, a pulse rate of 90 bpm, and he was afebrile. His abdomen was soft and not tender. His renal punch was negative. His rectal examination and other systemic examinations were unremarkable. His urine analysis showed the presence of leukocytes and a mild trace of blood.

An ultrasound of the abdomen showed bilateral mild to moderate hydronephrosis and hydroureter with no evidence of urinary stones. Cystoscopy examination revealed features of urethritis and cystitis. Renal computed tomography (CT) showed features of right pyelonephritis and bilateral obstructive uropathy, with no apparent cause identified (Figure 1). On the CT scan, there was mild intrahepatic duct dilation with no apparent distal obstruction. The renal profile was mildly deranged (urea: 14.1 mmol/L; sodium: 129 mmol/L; potassium: 3.2 mmol/L; creatinine: 136 µmol/L).

The patient was treated for urosepsis with bilateral obstructive uropathy. Intravenous antibiotics were started, and his condition initially improved. Since the patient also had elevated alkaline phosphatase (ALP: 1032u/L) and total bilirubin (TB: 51 µmol/L), he was referred to the hepatology team for further investigation, but the patient refused.

KEYWORDS: Ketamine abuse, cholestasis, cholangitis, liver cirrhosis, urinary tract complication

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Figure 1. A renal CT showed features of right pyelonephritis and bilateral obstructive uropathy.

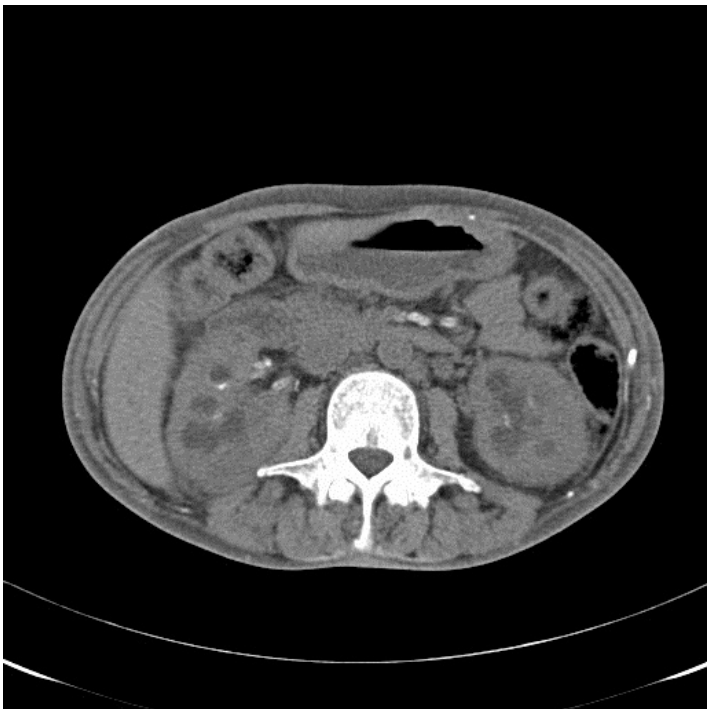
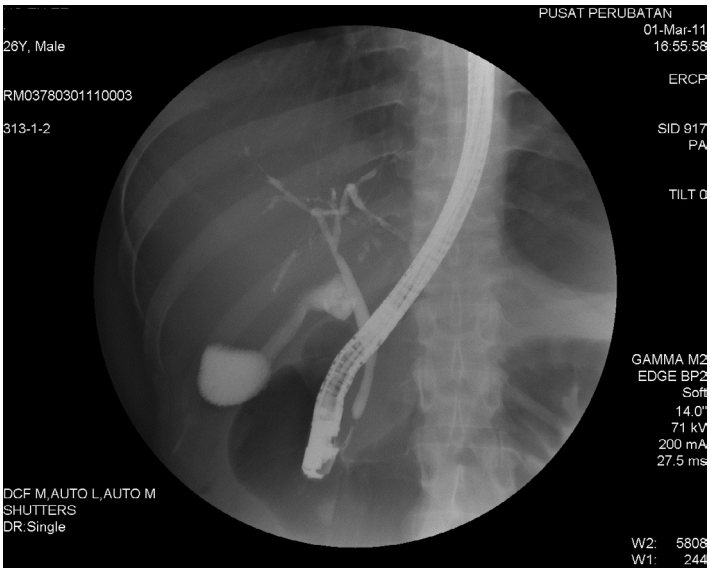


Figure 2. ERCP showed a beading appearance of the intrahepatic duct and irregular duct.



Subsequently, he was admitted to the hospital again on 2 different occasions with worsening urinary symptoms as well as worsening jaundice and generalized lethargy. A repeated renal CT showed bilateral pyelonephritis and the previous similar findings of bilateral obstructive uropathy. His hepatitis B/C and HIV screening were negative. A connective tissue disease screening, which tested anti-nuclear antibodies (ANA), anti-microsomal antibodies (AMA), and anti-smooth muscle antibodies (ASMA), was also normal.

About 16 months after the first presentation, he was admitted again with a fever, worsening jaundice, giddiness, and lethargy. A blood investigation showed extremely high alkaline phosphatase levels (ALP: 4985 u/L), a normal alanine transaminase level (ALT: 40 u/L), and raised serum bilirubin (total bilirubin: 120 µmol/L; indirect bilirubin: 15 µmol/L). The repeated CT of the abdomen showed similar findings of bilateral obstructive uropathy and pyelonephritis, and there were features of early liver cirrhosis with portal hypertension. The patient finally consented to an endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP). The findings were equivocal. The EUS showed a normal biliary tree and a normal pancreas. ERCP, however, showed beading of the intrahepatic duct and an irregular duct (Figure 2). Magnetic resonance cholangiopancreatography (MRCP) showed no dilated common bile duct (CBD) without a filling defect.

The patient finally admitted to abusing ketamine for the past 2 years. A liver biopsy was performed, and it showed portal and lobular hepatitis with cholestasis and hepatocyte damage. There was no evidence to suggest viral or autoimmune etiology, and there was no evidence of iron or copper deposition on the biopsy.

The patient was treated conservatively. Both his urinary and liver impairment improved to some extent after he stopped abusing ketamine but has failed to return to completely normal levels (ALP: 4985 u/L to 845 u/L; serum creatinine: 536 µmol/L to 339 µmol/L, after 4 months).

DISCUSSION

Ketamine is a N-methyl-D-aspartate (NMDA) receptor antagonist used clinically for the induction and maintenance of anesthesia. The use of ketamine in clinical settings was limited by the incidence of emergence reactions. Patients who are awakening from this anesthetic had reported psychotomimetic effects such as vivid dreams, hallucinations, delirium, and floating sensations [1].

Since the 1980s, ketamine has increased in recreational abuse by partygoers and youth in nightclubs or pubs. There has been reported cases of chronic ketamine abuse, leading to a

new clinical entity known as ketamine-associated ulcerative cystitis, which accounts for lower urinary tract symptoms, including frequency, urgency, dysuria, painful hematuria, hydronephrosis, and chronic kidney injury [2-4]. However, very little literature emphasizes chronic ketamine abuse as responsible for hepatobiliary dysfunction leading to cholestasis, cholangitis, and possible liver cirrhosis.

We report a young man who has ulcerative cystitis after chronic ketamine abuse, but also suffered from unexplained lethargy and cholangitis; e.g., fever, jaundice, and abdominal pain at the same time. As there was no initial knowledge of his drug abuse history, he was subjected to multiple investigations for his liver impairment. All these investigations had failed to establish the real etiology behind his condition. We believe there is an association between his liver impairment and cholangitic syndrome with chronic ketamine abuse. From the literature so far, there have been a few reported cases suggesting the association between chronic ketamine abuse with cholestasis and unexplained biliary duct dilation mimicking choledochal cysts [5,6].

Wong et al. had reported 3 patients with ketamine abuse of more than 1 year who suffered from urinary symptoms as well as cholestasis and fusiform dilatation of the biliary duct that resemble a choledochal cyst. Lo et al. also described 3 Caucasian men exhibiting ketamine abuse for more than 2 years who suffered from both urinary symptoms as well as cholestasis and a dilated biliary tree. A similar presentation was also noted in our patient who was also a chronic ketamine abuser for more than 2 years. Besides cholestasis, our patient had early liver cirrhosis.

The mechanism by which daily ketamine use leads to cholestasis and biliary dilatation remains unknown. Some authors have proposed that it might be the relaxation of the smooth muscles of the biliary tree that are responsible for cholestasis [6]. This is based on the theory that ketamine, an NMDA antagonist, may cause the relaxation of both the ureter smooth muscles and the biliary tree smooth muscles, leading to both hydronephrosis and cholestasis, respectively. The same author also proposed that ketamine's inhibitory effect on the dorsal motor nucleus of the vagus might cause reduced gallbladder motility and thus cholestasis.

Another author had suggested that the dysfunction of the sphincter of Oddi may be responsible for cholestasis and subsequently leads to the formation of benign biliary stricture [5]. However, a recent study by Varadarajulu et al. showed that there were no significant changes in flow resistance of the sphincter of Oddi in humans receiving ketamine for sedation [7].

Direct ketamine toxicity to the bladder and liver is another possible mechanism since hepatic microsomal enzymes metabolize this drug and excreted in the urine and bile [8,9]. The metabolite may have caused the toxicity effect to the urinary tract when it was metabolized, and it subsequently caused direct toxic effects to the liver and bile duct when excreted.

Clinically, most of the patients presented with epigastric or right hypochondriac pain with mild jaundice and fever after recurrent drug abuse. Known chronic abuse of ketamine is important in confirming the diagnosis, as there was no evidence of singular or short-term usage causing liver impairment. Blood investigations usually showed markedly raised alkaline phosphatase (ALP) and a less profound rise in alanine transaminase (ALT), suggesting that cholestasis is the more profound feature here than direct hepatocyte damage. The bilirubin level would usually be normal or borderline high. Apart from the abdominal pain, a patient may also present with general sickness, nausea or vomiting, and loss of appetite. All these patients also had lower urinary tract symptoms.

The abdomen ultrasound usually shows a normal gallbladder but with a dilated biliary tree, including intrahepatic duct dilatation such as our patient. However, in one of the previous cases reported, there was distal CBD stricture, which suggested that the drug might cause irreversible fibrosis of the biliary duct if the ketamine abuse is continuous. Otherwise, the effect of ketamine on biliary tree dilatation was reversible most of the time once abuse of the drug ended. Lo et al. has reported that radiography and hepatobiliary iminodiacetic acid (HIDA) scans show gallbladder dyskinesia resolution over time among patients who achieved abstinence.

ERCP and stenting was probably unnecessary and not helpful in these cases, unless the patient shows signs of biliary sepsis. Liver biopsy could be avoided if the history of ketamine abuse had been established earlier, as the procedure will not provide much additional information, and it poses potentially serious complications, such as bleeding from the biopsy site. However, most of these patients tend to go back to abusing the drug once their symptoms improve, leading to a recurrence of biliary stasis, which eventually leads to irreversible liver impairment.

In conclusion, chronic ketamine abuse not only causes urinary tract and kidney problems, it may also be responsible for hepatobiliary system impairment. The relevant authorities have to take the problem seriously, as the age group affected is mainly youths who are not aware of these complications. It is the responsibility of the health authorities to create awareness among the public that ketamine abuse is not safe. Physicians should have a high index of suspicion when a patient presents with lower urinary symptoms combined with deranged liver enzymes, jaundice, and abdominal pain. Serious complications like cholangitis and liver cirrhosis may be the end result if

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abstinence is not achieved.

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