Ketamine-induced sclerosing cholangitis: a case series

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Abstract

Background: **Ketamine-induced sclerosing cholangitis is an under-recognized but emerging condition, associated with chronic recreational ketamine use (1,2). While the bladder dysfunction related to ketamine abuse is well-documented, its hepatobiliary complications are less known (3). The disease mechanism remains unclear. It is suspected that ketamine has an effect on N-methyl-D-aspartate receptors in the bile duct smooth muscle, which contributes to chronic inflammation, fibrosis, and strictures. Patients present with abnormal liver function tests, imaging abnormalities, and aberrant liver biopsy. Management requires cessation of ketamine use, symptomatic treatment and close monitoring to prevent progression to cirrhosis (4-8).**

Cases: **This case series presents two cases of ketamine-induced sclerosing cholangitis in female patients, a demographic not typically represented in existing literature.**

Conclusion: **A multidisciplinary approach involving gastroenterologists, urologists, and psychiatrists is necessary (5). Long-term studies are needed to better understand the pathophysiology and to approve treatment and management of this disease. (**Acta gastroenterol belg., **2025**, 88, **271-276**).

Keywords: Ketamine, sclerosing cholangitis, cirrhosis.

Introduction

Ketamine-induced sclerosing cholangitis is poorly known, however increasingly identified as a disease associated with chronic recreational use of ketamine (1,2). Ketamine-induced bladder dysfunction is a disease that is better known among physicians (3).

While ketamine is known for its anesthetic purpose, long-term abuse can lead to severe bladder dysfunction but also serious hepatobiliary complications, like cholangitis and cholangiopathy. In the recreational context, ketamine is used at a higher dosage than in the medical field (4).

The mechanism behind the use of ketamine and the reported pathology is still unclear. What we do know is that the stimulation of N-methyl-D-aspartate (NMDA) receptors by ketamine in the bile duct smooth muscle, leads to chronic inflammation, fibrosis, strictures within both intrahepatic and extrahepatic bile ducts and in severe cases to cirrhosis (1,2,4-8).

Cases

Case 1

A 52-year old woman was admitted to the hospital after falling down the staircase in December of 2023. She suffered a subcapital femoral fracture on the right side. She was admitted to the orthopedics department and underwent a total hip replacement. Three days after the surgery we saw a cholestatic disturbed liver set. In the past she underwent a cholecystectomy and gastric banding, other than that she had a blank medical history.

Anamnesis uncovered that she recently suffered a viral infection. She recently took nitrofurantoin in the context of an urinary tract infection, estradiol/dydrogesterone for menopausal symptoms and iron supplements for iron deficiency. Regarding abuse she reported not to smoke, occasionally to consume alcohol and to use ketamine. Further systemic anamnesis was reassuring. Vital signs showed a temperature of 36.1 °C, blood pressure of 131/80 mmHg, blood oxygen saturation of 99% and a heart rate of 80 beats per minute. Examination was normal, without clinical signs of liver disease or hepatosplenomegaly. Blood sampling during her admission showed disturbed liver tests, especially at the beginning of the hospitalisation. An overview of the blood sampling during admission is shown in Table 1. Last blood draw before admission dated from 2014, but showed normal liver tests (AP 62 U/L, AST 16 U/L, ALT 7 U/L and GGT 13 U/L).

An additional ultrasound of the abdomen showed a state after cholecystectomy, without any other anomalies. Additional blood tests were taken; specifically: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), HIV 1 and 2, Epstein-barr virus (EBV) and cytomegalovirus (CMV). All hepatitis viruses and HIV tests were negative, EBV and CMV showed old infection parameters. Antinuclear antibody (ANA) test and anti-neutrophil cytoplasmic antibodies (ANCA) were negative. Iron levels were within normal range. Mitochondrial antibodies were also negative. Blood platelets count and INR were normal in every blood draw. IgG levels were normal. Livertests spontaneously became better during her admission and since she was asymptomatic she left the hospital on day 5.

Follow-up was provided after 2 weeks; we once again saw an asymptomatic patient with an increase of the cholestatically impaired liver set (bilirubin total 0.3 mg/dL, GGT 938 U/L, AP 582 U/L, AST 52 U/L

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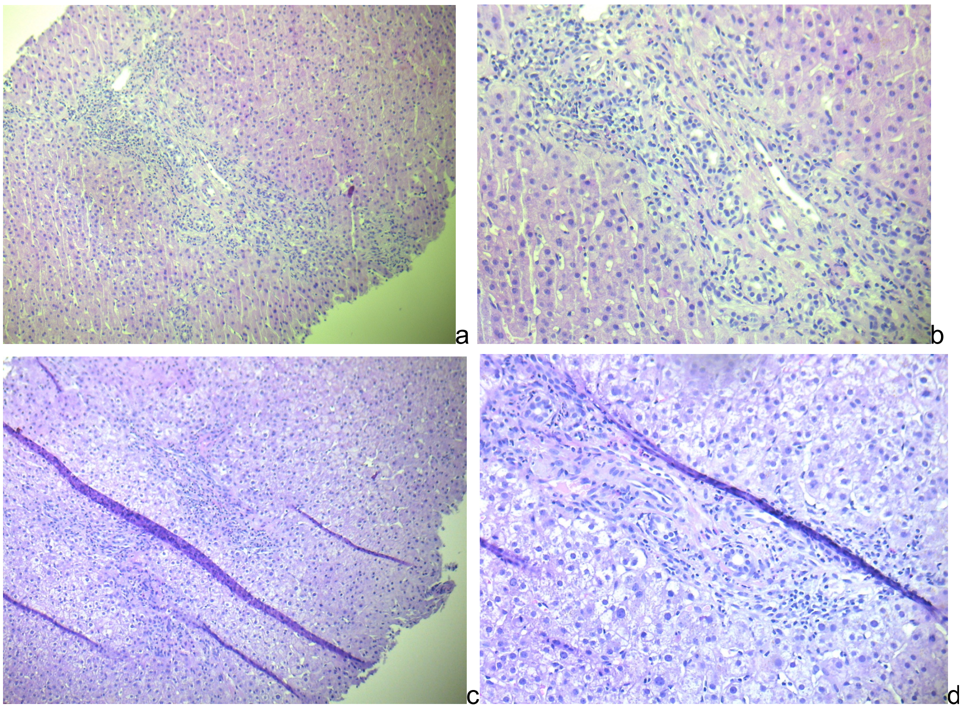

Figure 1. — Anatomopathological findings in liver biopsy of patient 1 (a,b) and patient 2 (c,d). a and c: x10. b and d: x20.

Table 1. — **Overview of blood sampling during admission, case 1.**

	Unit	Day 1	Day 3	Day 4	Day 5
Hemoglobin (Hb)	g/dL	12.4	9.1	7.6	9.4
CRP	mg/L	11.5	62.7	125.6	86.8
Bilirubin total	mg/dL	/	/	0.3	0.4
Gamma-glutamyltransferase (GGT)	U/L	667	509	434	506
Alkaline phosphatase (AP)	U/L	273	200	/	290
Aspartate aminotransferase (AST)	U/L	49	54	52	82
Alanine aminotransferase (ALT)	U/L	39	38	34	48

and ALT 44 U/L). Unfortunately the patient relapsed into ketamine use after discharge from the hospital. MRI of the liver was scheduled to exclude underlying conditions, and revealed no bile duct stenosis/structure and no choledocholithiasis. Given insufficient explanation of abnormal liver, additional liver biopsy was performed. This showed a good liver puncture cylinder with preserved architecture and well portal expansion due to ductular reaction. There was some bile duct damage with vacuolization and infiltration of lymphocytes within the epithelium. There was a discrete portal infiltrate in which some eosinophils were also recognizable. Clusters of ceroid macrophages were also present both in the portal fields as centrilobular. On PAS staining after diastasis, it is also clear that the basal membranes of the bile ducts are prominent. On keratin 7 staining there is substantial ductular reaction and cholestasis to midzonal with numerous cholestatic rosettes. The overall picture is a combination of sclerosing cholangitis with concomitant toxicity (eosinophils and clusters of centrolobular macrophages) (shown in figure 1 a and b).

Thus, diagnosis of sclerosing cholangitis but also for drug-induced liver injury (DILI) was made in April of 2024. Given her history of ketamine use, a diagnosis of ketamine-induced cholangitis was suggested. Nitrofurantoin can also be the cause of cholestasis and bile duct damage, however our patient only ingested nitrofurantoin for one week, without prior chronic use. The inflammatory conditions of her surgery could also contribute to the elevation of the cholestatic bloodwork. Small-duct primary sclerosing cholangitis (PSC) is also not excluded. Although the diagnostic criteria for small-duct PSC includes appropriate exclusion of other liver or biliary disease, such as DILI (9).

After discontinuing ketamine use, we saw favorable evolution of the liver set (bilirubin total 0.4 mg/dL, GGT 211 U/L, AP 263 U/L, AST 46 U/L, ALT 43 U/L), raising the suspicion of our diagnosis. At the time she discontinued her ketamine abuse for two weeks. During her gastroenterological follow-up, she also reported urological symptoms. Urological examination was normal. These symptoms also got better after discontinuing her ketamine use.

Unfortunately she did not show up for her follow-up consultation in July of 2024. She did still present at the urology consultation where she mentioned that her ketamine use had restarted.

Case 2

In March of 2024, a 24-year old woman was referred by her general practitioner because of weight loss (10 kg) in 1 month, despite sufficient intake. She had been feeling tired and generally unwell for several days. Further systemic history-taking was normal. She was actively smoking and used 4 grams of paracetamol a day for a couple of months. Lab results were significantly altered with a total bilirubin of 0.2 mg/dL, AST of 63 U/L, ALT of 68 U/L, AP of 652 U/L and GGT of 1185 U/L. Blood platelets count and INR were normal. ANA and ANCA tests were negative. Iron levels were within normal range. Mitochondrial antibodies were also negative. HAV, HBV, HCV, EBV and Toxoplasma testing were all negative. Alpha 1-antitrypsin levels were also normal, as were IgA, IgG4 and IgM levels. Abdominal ultrasound was performed and showed a picture of hepatic steatosis. She was advised to stop the intake of paracetamol. MRI of the liver was performed and showed caliber variations in the intrahepatic bile ducts mainly on the left and slight stenosis at the level of the distal main bile duct, ostially at the ductus hepaticus dexter. It also revealed edematous changes (inflammation) subcapsular in the right liver with hepatomegaly and multiple reactionally enlarged lymph nodes in the hepatic hilus. The MRI was fitting for a primary sclerosing cholangitis (shown in figure 2).

In April of 2024 she presented in the emergency room because of abdominal pain and diarrhea with rapid deterioration over the last week. She did not document any fever, but mentioned notable pollakiuria, without pain or burning. Initially, she denied use of alcohol and drugs, but afterwards did admit to ethyl, ketamine, cocaine and cannabis use in the recent past. On top of that, she used tramadol and diclofenac daily for her bladder pain. She was admitted to the gastroenterology department. Overview of her lab results during the hospitalisation are shown in Table 2. A urine sample was positive for ketamine. A colonoscopy was performed and showed no signs of inflammatory bowel disease (IBD). MRI of the pancreas showed no signs of pancreatitis. During hospitalisation liver biopsies were obtained. Anatomopathological examination of the biopsy showed damaged bile ducts with lymphocytes between the epithelium, picnosis of epithelial cells or vacuolization. There was a ductular reaction where the porta field expanded somewhat but no septa were formed yet.

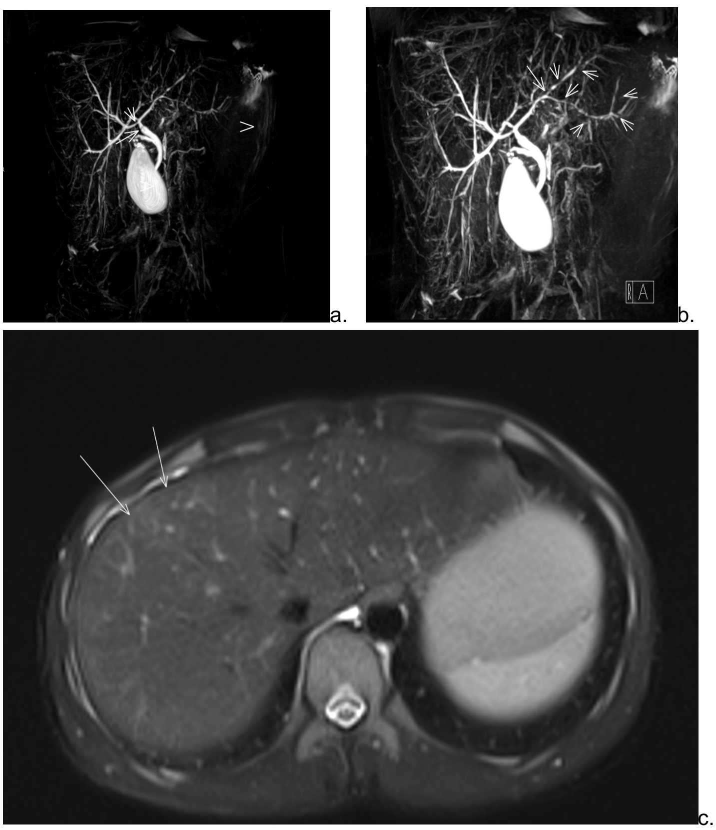

Figure 2. — Magnetic Resonance Imaging (MRI) of patient 2. a.: slight stenosis at the level of the distal main bile duct, ostially at the ductus hepaticus dexter. b.: caliber variations in the left intrahepatic bile ducts. c.: edematous changes (inflammation) subcapsular in the right liver with hepatomegaly.

Table 2. — **Overview of blood sampling during admission in 04-2024, case 2.**

	Unit	Day 1	Day 2	Day 4	Day 8
Hemoglobin (Hb)	g/dL	11.5	11.1	9.8	10.7
CRP	mg/L	42	35.2	9.6	3.9
Bilirubin total	mg/dL	0.6	0.2	0.2	0.2
Gamma-glutamyltransferase (GGT)	U/L	1806	1610	1343	1127
Alkaline phosphatase (AP)	U/L	1092	947	716	633
Aspartate aminotransferase (AST)	U/L	91	90	74	48
Alanine aminotransferase (ALT)	U/L	173	150	113	83

On keratin 7 we saw incipient cholestasis. On PAS staining after amylase, the basal membranes were clearly thickened. There was no obvious ductopenia. The whole is diagnostic of sclerosing cholangitis with periportal fibrosis (shown in figure 1 c and d). After a hospitalisation of 8 days she was discharged.

A follow-up consultation was provided after 3 weeks. Unfortunately, we saw a further deterioration of our patient. She experienced abdominal pain, difficulty eating, night sweats and further weight loss. Her stool frequency was increased. The bladder symptoms (pain and frequency) remained very present, resulting in urinary incontinence. She admitted to still smoking cigarettes but also used ketamine last weekend. Other legal and illegal drug using was no longer active. She was readmitted to the gastroenterology department. The evolution of infectious parameters and liverset during hospitalisation are shown in Table 3.

To make sure there was no other cause underlying the anorexia, a gastroscopy was performed, showing no anomalies. A CT-scan of the brain was performed to rule out cerebral malignancies.

After a hospitalisation of 2 weeks, with administration of tube feeding through a nasogastric probe, we observed a favourable evolution of the clinical and biochemical picture. Our patient was referred to our colleagues of Urology and Nephrology for her bladder symptom. But also to a Psychiatrist to guide her in stopping the ketamine abuse. A follow-up appointment was planned 5 weeks after discharge from the hospital, sadly she did not show up.

We did however see her in August of 2024 in our emergency department; because of severe abdominal pain. In the time that she was lost in follow-up, she underwent derivative urological surgery, specifically a supratrigonal cystectomy with insertion of a pouch. The abdominal pain she presented with in August of 2024 was found to have its origin in a perforation at the level of the entero-enteric anastomosis, which was surgically restored. Liver tests on the blood sample taken at the emergency room were better than all the previous testing of this year (AP 388 U/L, ALT 31 U/L, GGT 495 U/L, bilirubin total 0.3 mg/dL). Suggesting that she is no longer using ketamine and her cholestatic liver abnormalities are normalising.

Discussion

The first report on the association of liver injury with ketamine dates back to 1980, we are now 40 years later and there is still a lot to uncover. What we can derive from these 2 cases and the available evidence is that ketamine-induced sclerosing cholangitis is a severe condition, worthy of our attention.

Patients usually present without symptoms but with abnormal liver tests (10), showing elevated enzymes like gamma-glutamyl transferase (GGT) and alkaline phosphatase (AP) (2,11). Over time, as bile duct strictures aggravate, patients can develop cholangitis. Imaging may reveal bile duct dilatation and beading, similar to primary sclerosing cholangitis, but could also be completely normal (5).

While a lot is still unknown, case reports in the past have shown that cessation of ketamine can diminish further damage (2,4,5,10,12). Medication may be prescribed to reduce inflammation and manage pain. A close follow-up is also advised. But in severe cases, endoscopic interventions, such as bile duct stenting, may be necessary to relieve strictures and symptoms. Management is complex, often requiring a multidisciplinary approach involving gastroenterologists, urologists, and psychiatrists.

Table 3. — **Overview of blood sampling during admission in 05-2024, case 2.**

	Unit	Day 1	Day 5	Day 8	Day 11
Hemoglobin (Hb)	g/dL	11.2	10.7	/	10.4
CRP	mg/L	79.8	27.3	/	16.9
Bilirubin total	mg/dL	0.3	0.2	0.2	0.1
Gamma-glutamyltransferase (GGT)	U/L	1692	1799	1154	987
Alkaline phosphatase (AP)	U/L	866	1007	659	576
Aspartate aminotransferase (AST)	U/L	155	162	68	47
Alanine aminotransferase (ALT)	U/L	180	222	124	71

Ketamine

Ketamine is a dissociative anesthetic, initially developed for medical purposes, but its effects range from analgesic to hallucinations, depending on its dose and context of use (4). Ketamine is metabolised in the liver and excreted by the kidney. Despite its legitimate medical uses, ketamine has significant abuse potential, particularly for its euphoric and hallucinogenic effects (4). It is also not surprising that the side effects, such as bladder and cholestatic liver damage, are also dose and quantity dependent.

Ketamine works by blocking N-methyl-D-aspartate (NMDA) receptors in the brain, which are involved in pain transmission and synaptic plasticity. The mechanism behind the development of cholangitis in patients with ketamine abuse is suspected to be the result of a direct action on the biliary smooth muscle or central action (9,12-14). However a prospective evaluation by Varadarajulu S. et al. in which ketamine was administered to patients had no significant effect on the motility of the sphincter of Oddi (7). Nevertheless this evaluation does not reflect the reality, as ketamine abusers had chronic and repeated exposure (11).

Diagnosis

The most common first presentation is an asymptomatic patient with deranged liver tests, but abdominal pain can be present (11). Jaundice only occurs when the hepatobiliary tract is obstructed. A review of case reports showed a correlation in severity of the cholangitis if patients experience urinary symptoms (11). Only one of our patients experienced abdominal pain, both did experience urinary symptoms. We also saw in our cases that the patient with more urinary symptoms had the more deranged liverset and abnormal imaging of the hepatobiliary tract.

Regarding imaging, more specifically magnetic resonance imaging (MRI), Seto W.K. et al documented that recreational inhalation of ketamine can result in anomalies of the biliary system. They reported 4 types: normal imaging, diffuse extrahepatic duct dilatation, fusiform extrahepatic duct dilatation with distal tapering and intrahepatic duct dilatation or beading with normal extrahepatic ducts. Seto W.K. et al revealed that AP levels had a predictive value for biliary tract anomalies and the presence of urinary tract symptoms was a risk factor. In contrast, duration of ketamine exposure was not correlated. They concluded that ketamine-induced cholangiopathy may be reversible after abstinence, but that an evolution towards secondary biliary cirrhosis is possible after prolonged exposure (5).

A final important part of the diagnosis is biopsy. In our knowledge there has not been a systematic review on biopsy findings. However several case reports reported their anatomopathological findings, being similar to those of primary sclerosing cholangitis.

Critical review of our case series

In both cases, the diagnosis remains uncertain. In Case 1 MRI was normal and anatomopathological study showed findings compatible with sclerosing cholangitis but also for drug-induced liver injury (DILI). Given her history of ketamine use, a diagnosis of ketamine-induced cholangitis was suggested. However nitrofurantoin can also be the cause of cholestasis and bile duct damage. Nevertheless, our patient only ingested nitrofurantoin for one week, without prior chronic use. In addition, the inflammatory conditions of her surgery could also contribute to the elevation of the cholestatic bloodwork. Lastly, small-duct primary sclerosing cholangitis (PSC) is also not excluded. Although the diagnostic criteria for small-duct PSC includes appropriate exclusion of other liver or biliary disease, such as DILI (9).

In Case 2 we are also still dealing with multiple differential diagnoses. PSC is not excluded, however since we did not document any signs of inflammatory bowel syndrome less likely. In this case, there was also a combination of substance abuse complicating the diagnosis. In retrospect, malignancies were also not excluded by PET CT.

So what makes us suspect that these syndromes are ketamine related anyway? In both cases the cessation of ketamine use led to an improvement of the hepatic and cholestatic tests, suggesting that there is a correlation. In addition, RUCAM-scores (Roussel Uclaf Causality Assessment Method in Drug Induced Liver Injury) were calculated for both patients (15). Both scored "+3", which means the causality is categorised as "possible".

Management

Given that there are at present no long-term longitudinal studies available we can not give an evidence based advice in management on ketamine-induced sclerosing cholangitis. We can however learn from the published case reports.

What all physicians agree upon is that complete cessation of ketamine abuse is primordial to prevent further damage. Coping with the symptoms associated with a cholestatically impaired liver can be medication or an endoscopic intervention (2,5,10-12,16). But most importantly a close follow-up is necessary, being it common knowledge that if cirrhosis occurs secondary to the long-term ketamine abuse, the resulting damage is irreversible. Knowing these are mostly very young patients, prevention remains very important.

What makes this case series different?

Our case series differs from previous ones, because we reported two female patients and most of the published cases involved male patients. In addition our cases relate to European inhabitants, while most case reports and reviews available to date are based on an Asian population.

Conclusion

We wanted to raise awareness for this relatively rare but emerging condition linked to the recreational use of ketamine. Especially since when not recognised as disease, it can lead to irreversible liver cirrhosis.

We conclude that a systematic approach with history taking, clinical examination, blood samples, abdominal ultrasound, MRI of the liver and liver biopsy remain the best course of action to exclude other (treatable) diseases.

Long-term studies or retrospective studies are necessary to evaluate the best course of treatment, to evaluate the consequences and impact of this disease and to uncover the still remaining uncertainties of the pathophysiology.

Treatment and follow-up will require a multidisciplinary approach involving gastro-enterologists, urologists, and psychiatrists.

Declarations

Conflict of interest statement: All authors declare that there were no conflicts of interest during the process of this case series.

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