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Case Report

Ketamine-induced cystitis: A case report and literature review ☆,☆☆,★

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ABSTRACT

Ketamine, a dissociative anesthetic drug, has gained popularity as a recreational substance, particularly among young adults. However, chronic ketamine abuse can lead to various complications including ketamine-induced cystitis. We present the case of a 46-year-old Caucasian male with a history of HIV infection and daily recreational ketamine use for 7 months, who was admitted to the emergency room with hypogastric pain and hematuria. Laboratory examinations and contrast-enhanced abdominal CT tomography revealed significant irregular circumferential thickening of both ureters, substantial bilateral pyeloureteral ectasia, and a bladder with markedly thickened walls. Bilateral flexible ureteropyeloscopy, bladder transurethral resection, and bladder fulguration were performed, and pathology confirmed the diagnosis of ketamine-induced cystitis. Treatment consisted of ketamine withdrawal, pain relief, and support from psychiatrists and urologists. The patient's symptoms improved and he was discharged without complications. This case highlights the importance of recognizing the potential adverse effects of recreational ketamine use and the need for a multidisciplinary approach to managing ketamine-induced cystitis. Further research is necessary

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to elucidate the precise mechanisms underlying this condition and develop effective prevention and treatment strategies.

Introduction/Background

Ketamine is a dissociative anesthetic drug that is commonly used in medical settings because of its analgesic and anesthetic properties. However, recreational use of ketamine has become increasingly prevalent in recent years, particularly among young adults. A potential complication of recreational ketamine use is ketamine-induced cystitis, a condition characterized by inflammation of the bladder and ureters.

Patient description

The patient was a 46-year-old Caucasian male with a history of HIV infection and daily recreational use of ketamine for the last one since 7 months ago. He was admitted to the emergency room due to 2 days of hypogastric pain and hematuria and was agitated due to the use of inhaled ketamine.

Initial laboratory examinations were performed: Hemoglobin 15.6 g/dL Hematocrit, 43.4%; leukocytes, 9910 mm^3; platelets 305000 creatinine 0.96 mg/dL C-reactive protein 1.38 mg/dL (0.06-0.5 mg/dL) Sodium: 136 (137-145 mEq/L) potassium 2.8 mEq/L (3.6-5 mEq/L) INR 0.98 thromboplastin partial time 29.3 s (25.1-36.5 seg).

The patient's urine analysis was cloudy, reddish pH 6 density 1020 occult blood 250 nitrite negative proteins 500 normal glucose negative pigment fresh red blood cells greater than 20 per high-power field. No germs. M. tuberculosis was not detected by chain reaction PCR and Urine BK. negative urine culture.

Nonreactive VDRL, hepatitis C antibody, and hepatitis B surface antigen test results were negative. The HIV viral load was undetectable, reflecting a controlled disease.

Contrast-enhanced abdominal CT (Figs. 1 and 2) revealed significant, irregular circumferential thickening of both ureters with inferior predominance, as well as substantial bilateral pyeloureteral ectasia with discrete right predominance. The bladder was partially distended, with markedly thickened walls that hypercaptured the contrast medium, reaching a thickness of 9 mm.

Based on these findings, bilateral flexible ureteropyeloscopy plus bladder transurethral resection (TUR) and bladder fulguration were performed: healthy anterior and posterior urethra, with urothelial edema and hyperemia, no HEU, nonobstructive high neck, bladder with orthotopic meatuses, upon visualization of the bladder evidence of thickening of the bottom of the bladder, side walls, and roof; mild trabeculation; generalized inflammatory changes; no clear evidence of mass; normal meatus on left ureteroscopy; ureter dilated distally with no visible mass in the ureter or cavities, on right ureteroscopy or changes marked inflammation of the distal ureter, without visualization of lesions. Multiple bladder samples were collected, and cytology was performed (Fig. 3), which showed reactive changes in the surface epithelium and edema, dilated and congestive vessels, and lymphoplasmacytic infiltration with polymorphonuclear neutrophils. No neoplasia was observed in the serial sections.

The diagnosis of ketamine-induced cystitis was based on the clinical findings, results of contrast-enhanced abdominal CT scans, and pathology.

The treatment consisted of withdrawal of ketamine and pain relief (visceral and neuropathic) with antispasmodics, neuromodulators, and transdermal opioids (buprenorphine). He also received support from the psychiatrists and urologists.

The patient was discharged after several days of treatment and follow-ups. The patient's symptoms improved and there were no complications.

Discussion

Ketamine is a pharmaceutical drug with both analgesic and anesthetic properties. It induces anesthesia by producing analgesia with altered consciousness, while maintaining airway tone, respiratory drive, and hemodynamic stability [1]. At lower doses, it has psychoactive properties and has gained popularity as a recreational drug [1].

Ketamine is a noncompetitive N-methyl-D-aspartic acid receptor complex antagonist synthesized in 1962 and first used in humans in 1965 to induce and maintain anesthesia as well as for its potent analgesic properties [2,3].

The precise mechanism of action of ketamine is not entirely understood; however, it is thought to act on NMDA receptors, sodium channels, and HCN1 receptors [1]. Additionally, the drug exhibits a rapid absorption rate, with peak plasma concentrations attained within 22-120 minutes of administration depending on the route of administration [1]. Ketamine is extensively metabolized in the liver to form several active metabolites [1].

Ketamine is primarily eliminated by the kidneys, and has a half-life of 1.5-5 hours [1].

Acute adverse effects include impaired consciousness, dizziness, irrational behavior, hallucinations, abdominal pain, and vomiting [1].

Chronic effects include impaired verbal information processing, cystitis, and cholangiopathy [1].

Its excellent cardiovascular stability and dissociative effects make it an ideal choice for conscious sedation [1].

Ketamine abuse was first reported in the United States in the early 1970s [1,4]. Since then, it has gained popularity as a drug of abuse in clubbing, dancing, and rave-party scenes. According to estimates, the annual prevalence of ketamine use among the United States population between 2015 and

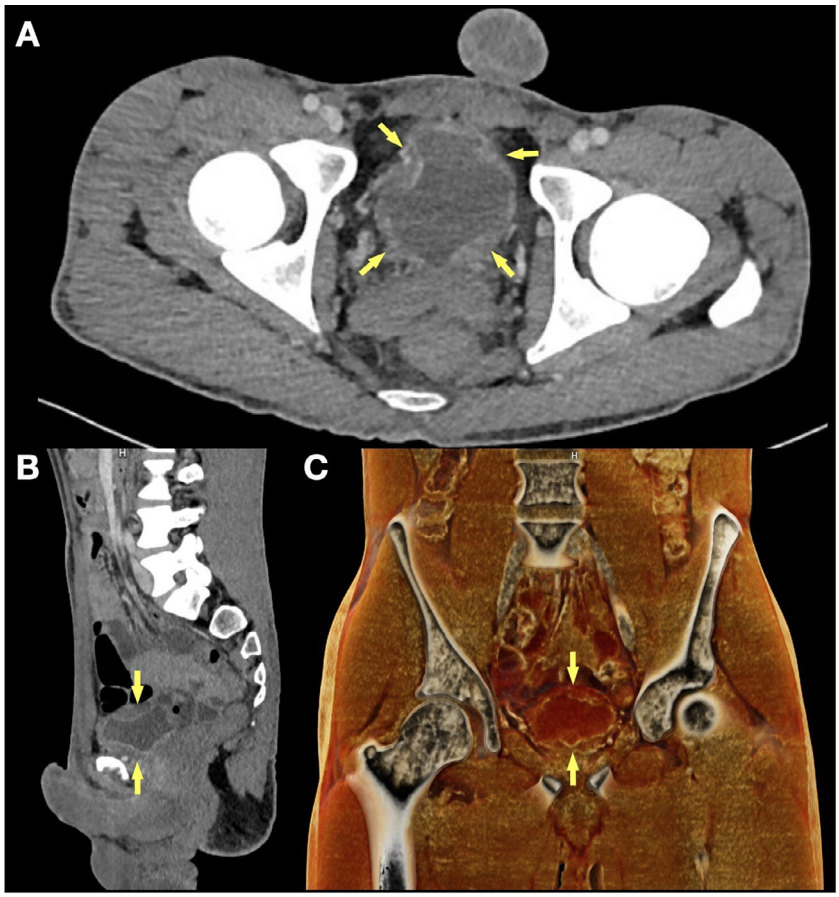

Fig. 1 – (A and B) show axial multiplanar reconstruction and volume rendering showing a bladder with thickened walls and trabeculation (yellow arrows). (C and D) show coronal and volumetric multiplanar reconstructions, showing dilation and linear enhancement of the ureters, respectively.

2019 was approximately 0.13%, which translates to a significant proportion of the population [5].

The powdered form of ketamine is typically snorted and users often report feelings of contentedness, increased sociability, and psychedelic effects. However, they also experience negative effects such as paranoia, depression, and loss of control [2].

Heavy ketamine users may develop a condition known as ketamine-induced cystitis, which can cause severe lower urinary tract symptoms, hematuria, and pelvic pain. The exact timing of the onset of this condition is not always predictable, and there is a limited understanding of the relationship between long-term use, dose, and the development of ketamine-induced cystitis [2].

A review of 3 surveys conducted with frequent users indicated that as many as one-third of them experienced symptoms of the lower urinary tract [1].

Prolonged abuse can result in hydronephrosis, a contracted bladder, ureteral stenosis, and vesicoureteral reflux [4].

Ketamine can also affect the kidneys, resulting in interstitial nephritis and papillary necrosis [4]. Some patients also demonstrate deteriorating renal function [6].

The precise mechanisms underlying ketamine cystitis remain unclear; however, several hypotheses have been proposed, including adverse effects on the urothelium, disruption of microvascular circulation, and immune system activation [2]. It is also linked to nerve fiber infiltration, changes in ion channel expression, urothelial barrier compromise, increased oxidative stress, altered gene expression, inflammation, dysregulation of autophagy, and inhibition of angiogenesis in the bladder. Studies have shown that ketamine treatment results in increased levels of cytochrome c, disturbances in the Akt/ERK1/2/GSK3ß signaling pathway, and impaired urothelial barrier function and apoptosis [3].

The diagnosis of ketamine-induced cystitis (KC) is mainly established by anamnesis, and a high index of suspicion should be present in the presence of a young adult complaining of lower urinary tract symptoms (LUTS) and a history of long-term ketamine abuse [2,4,7].

Investigations included computed tomography, urography, cystoscopy, and urodynamic studies [2].

Ultrasound has demonstrated small bladder volume and wall thickening [8,9].

CT revealed diffuse bladder wall thickening, mucosal enhancement, and perivesical inflammation [8,9].

Some patients have upper urinary tract involvement, including ureteric wall thickening and enhancement [8,9].

Cystoscopy has revealed inflammatory changes in the bladder, including ulceration of the mucosa, erythema, inflammation, fibrosis, and bleeding [10,11].

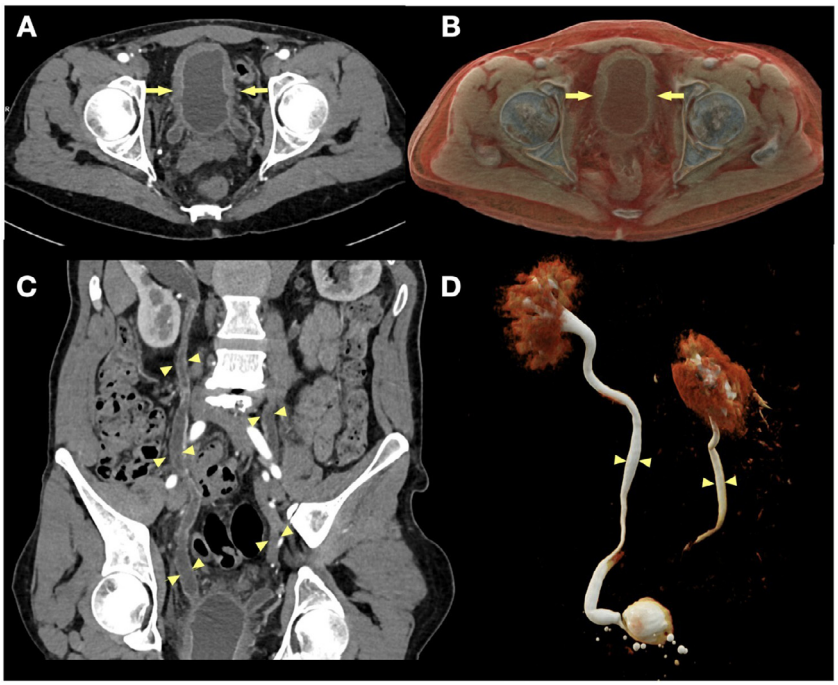

Fig. 2 – (A) shows the axial multiplanar reconstruction. (B) Sagittal multiplanar reconstruction. (C) Coronal volume-rendering technique. Bladder with irregularly thickened walls, luminal enhancement, and trabeculation (yellow arrowheads).

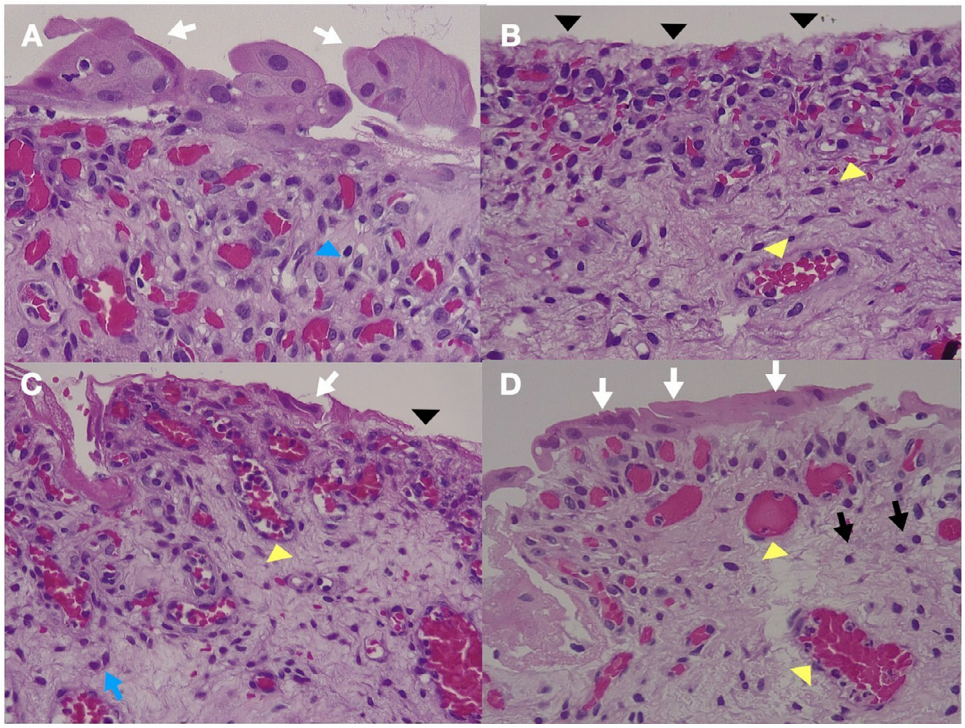

Fig. 3 – Histological examination of the bladder: high-power 400x hematoxylin-Eosin (H&E) staining. (A) Reactive urothelial cells (white arrows), stroma congestion (blue arrowheads). (B) Sphacelated epithelium (black arrowheads) and stromal congestion with dilated vessels (yellow arrowheads). (C) Reactive urothelial cells (white arrows), sphacelated epithelium (black arrowheads), dilated and congestive vessels (yellow arrowheads), and reactive stromal fibroblasts (blue arrow). (D) Reactive urothelial cells (white arrows) with dilated and congested vessels (yellow arrowheads) and plasmocytes (black arrows).

Sections of the uroepithelial mucosa become denuded with cellular infiltrates, notably neutrophils, eosinophils, lymphocytes, and mast cells, within the mucosa and underlying lamina propria [10,11]. Tissue granulation is also observed within the lamina propria. In severe cases, ulcerative cystitis can progress to cystitis glandularis and may even lead to the development of carcinomas accompanied by changes such as squamous and nephrogenic metaplasia [6,12].

Ketamine cystitis mimics carcinoma in situ but can be distinguished by the negative expression of CK20 [2].

Currently, there are no validated treatment regimens for ketamine-induced cystitis. However, immediate and total cessation of ketamine can prevent disease progression, and almost half of patients who abstain from ketamine report symptom improvement [2,7,13,14].

Traditionally, treatment strategies have begun with more conservative options targeted at symptom control and have then advanced toward more invasive and combined treatments. Beginning with oral medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and paracetamol, which are effective in relieving pain, can be administered either alone or in combination with antimuscarinic medications such as solifenacin or oxybutynin to treat bladder spasms [1]. However, when patients are resistant to such treatments, opioids, such as buprenorphine in patches, or neuromodulators, such as gabapentin or pregabalin, which are typically prescribed for neuropathic pain, have shown some effectiveness. Additionally, off-label uses for drugs include tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, and lidocaine [1,2,13].

Chronic Pain Teams frequently administer a combination of medications, such as intravesical instillation of heparin or hyaluronic acid, to repair the glycosaminoglycan layer and anti-inflammatory agents, such as corticosteroids, dimethyl sulfoxide, analgesics, and local anesthetics [1]. Additionally, they may recommend urine alkalinization with sodium bicarbonate as a part of the treatment for interstitial cystitis or bladder pain syndrome. Nonresponders to bladder instillations may require surgical intervention, including subtotal cystectomy and orthoptic reconstruction [1,13].

Future studies should assess the potential of these emerging therapies and other drugs to treat chronic pain in KIC [13].

Long-term follow-up is essential because it is unknown whether chronic inflammatory processes predispose patients to malignant urinary tract diseases [2].

Conclusion

Ketamine-induced cystitis is a potential complication of recreational ketamine use. This condition can lead to symptoms, such as hypogastric pain, hematuria, and thickening of the ureters and bladder walls. The diagnosis of ketamine-induced cystitis is based on clinical findings and imaging studies such as contrast-enhanced abdominal CT scans. Treatment typically involves supportive care including pain management and fluid replacement.

Author contributions

NT, JDQ, MGD, JFB, CJSE, GM, and BR contributed to the design and implementation of the research; NT, JFB, MGD, JDQ, CJSE, BR, and GT contributed to the analysis of the results and to the writing of the manuscript. NT and JDQ conceived and supervised the original project.

Patient consent

In this report, we obtained informed consent from the patients and their family members for publication of their personal and medical information. We have taken measures to ensure the confidentiality of the patient's identity and removed any identifying information from the report.

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