

# Ketamine-Induced Uropathy: The Detrimental Effects of Chronic Ketamine Abuse Beyond the Bladder-A Case Report with a Brief Literature Review

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## Abstract

Bladder toxicity associated with high-dose recreational ketamine use, is well-documented. However, the upper tract merits more attention because hydronephrosis may not solely stem from impaired bladder compliance and vesicoureteral reflux. We report an autopsy case of a 28-year-old man with extensive upper tract pathology, indicating that the direct effects of ketamine and its metabolites extend beyond the bladder. Urothelial denudation, chronic transmural inflammation, ureteric fibrosis, interstitial nephritis, and papillary necrosis in the kidney were observed. Our findings underscore the importance of assessing ureteral integrity before bladder surgery given that unrecognized strictures may complicate reconstructive procedures and lead to kidney failure.

**Keywords:** Pathology, reconstructive urology, ketamine, ureteral strictures, interstitial nephritis, papillary

## Introduction

Due to its dissociative and hallucinogenic effects, ketamine has gained popularity as a recreational drug. In Europe, wastewater analyses reflect a recreational use pattern in the majority of tested cities, with the highest mass loads of ketamine residues detected in cities in Belgium, France, the Netherlands, and Spain (1).

In parallel with increased consumption, more patients present with painful bladder symptoms. Ketamine-associated ulcerative cystitis was first reported in 2007 (2). The clinical presentation of chronic ketamine abuse can be diverse and frequently includes cystitis-like complaints and increased urinary frequency. Results from cystoscopy, bladder biopsies, and video-urodynamic studies have illustrated various degrees of epithelial inflammation, neovascularization, and reductions in functional and cystometric bladder capacities (3,4). Pathological findings in the urinary bladder are variable and are related to the progression of urinary inflammation. An overview of the reported symptoms

and technical findings is summarized in Table 1. While bladder toxicity has become widely recognized, it is increasingly evident that several high-dose recreational users also develop severe hydronephrosis and kidney failure. This is often attributed to the small-capacity high-pressure bladder; nevertheless, a direct toxic effect on the upper tract is suspected. To illustrate the effect of ketamine beyond the urinary bladder, we present the autopsy findings of a 28-year-old ketamine abuser.

## Case Presentation

A 28-year-old man who was known for chronic ketamine abuse (more than 4 grams daily) and suffering from related bladder pain and incontinence was found dead at home. A medicolegal autopsy revealed ketamine intoxication (>2500ng/mL blood) as the cause of death. Upon evisceration, localization of the bladder was challenging because of adhesions and firmness of surrounding adipose tissue, suggesting an extended inflammatory process to the adjacent peritoneum. As a result,

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pelvic structures were removed en bloc and gross after complete fixation. Representative tissue samples were obtained and further processed according to accredited standard protocols (formalin-fixed paraffin-embedded slides and hematoxylin and eosin staining). The slides were reviewed by experienced urological pathologists.

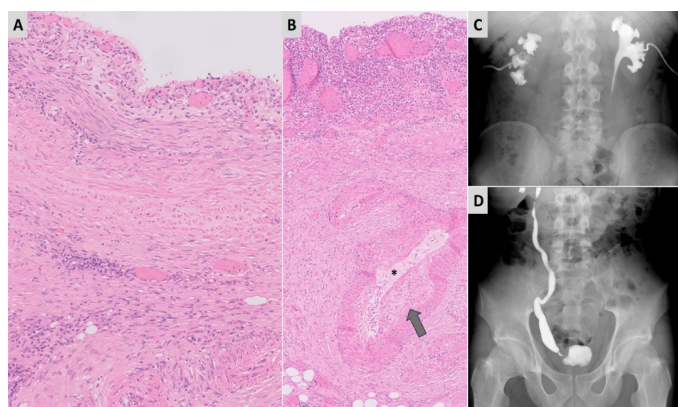
Subsequent histopathological analyses revealed extensive bladder and upper urinary tract pathology. Both kidneys exhibited gross and microscopic abnormalities. The left kidney showed yellow-brown mucus in the renal pelvis along with cysts, and the right kidney harbored cysts filled with brown fluid. Scattered calcifications were observed throughout both kidneys, predominantly localized at the medullary pyramids. Microscopic evaluation (Figure 1A) revealed congested parenchyma with abundant interstitial inflammation and papillary necrosis.

Both ureters macroscopically appeared normal, but microscopic examination (Figure 1B) revealed bilateral extensive erosion of the urothelium with neutrophilic granulocytes, indicating purulent inflammation affecting the mucosa and submucosa. The muscularis propria showed chronic (lymphocytic) infiltrates, increased vascularization, and marked fibrosis and reactive changes extending to the surrounding fat tissue. However, the most striking were the proliferative changes observed within the media layer of blood vessel walls, which were thickened by intimal fibrosis, resulting in narrowing of the lumen (Figure 1B). These findings leading to segmental

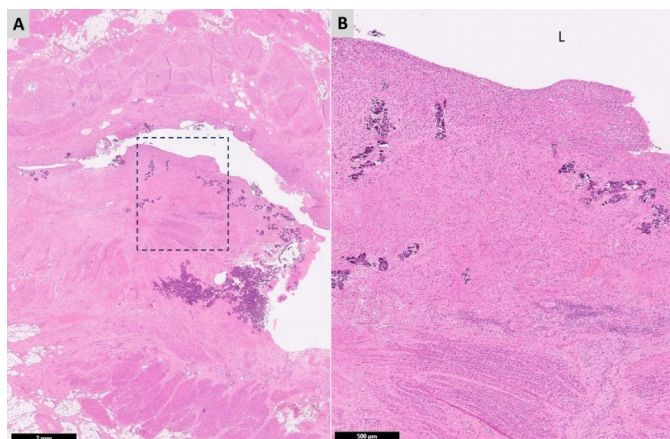
ureteral strictures could explain the segmental beading or even complete ureteral obstruction seen on ureterogram (Figure 1C).

Upon grossing, the bladder wall was contracted, fibrous, and encrusted with abundant calcifications. Microscopic evaluation confirmed these findings (Figure 2). Furthermore, urothelial erosion with focal replacement using granulation tissue or necrotic debris was observed. Additionally, detrusor mastocytosis, perineuritis, mycotic infection, and bacterial infection were observed. These observations were confirmed through supplementary staining (GRAM staining to detect and differentiate bacteria, Grocott's to detect fungi, CD117 to detect and count mast cells, mast cell tryptase to measure the activity of mast cells and their role in the inflammatory reaction, and S-100 to visualize nerve fibers). Scattered eosinophils were present but were not significantly increased for the diagnosis of interstitial cystitis.

Overall, the findings illustrate the toxicity of ketamine with clear upper and lower urinary tract involvement, resulting in inflammatory and fibrotic responses. An overview of the histological features of ketamine-induced uropathy is provided in Table 2. The Ethics Committee of the Antwerp University Hospital (UZA)/UAntwerpen provided a waiver of informed consent for publication of this postmortem case report, as this examination was conducted within a judicial context.



**Figure 1.** Alterations attributable to ketamine toxicity in the pyelum and ureter (hematoxylin and eosin staining, 20x magnification). A) The pyelum presents with a relatively thin epithelium and areas of denudation, accompanied by an underlying lymphocytic infiltrate, indicative of chronic inflammation. The renal parenchyma shows congestion along with abundant interstitial inflammation. B) Urothelial denudation accompanied by granulation tissue and fibrosis is a reparative or reactive process. Mixed inflammatory infiltrates extend toward the nerve bundles (perineuritis-not visible on this magnification) and surrounding adipose tissue (transmural inflammation). Additionally, notable proliferative changes are observed within the media layer of blood vessel walls, which are thickened by intimal fibrosis (arrow), resulting in narrowing of the lumen (asterisk). C, D) Illustration of severe proximal strictures and D) hockey stick ureter



**Figure 2.** Characteristic alterations attributable to ketamine toxicity in the bladder (hematoxylin and eosin staining). A) Disruption of architecture is evident at low magnification. The indicated area is enlarged in figure B. Bar=2 mm. B) 20x magnification of the insert (dashed line). Extensive urothelial denudation (erosion) is accompanied by granulation tissue replacement. Diffuse to extensive areas of calcification (dark purple irregular deposits) are observed, extending through approximately half of the detrusor muscle, with the inner half being severely fibrotic. An inflammatory infiltrate (mainly lymphocytes and occasional eosinophils) is seen throughout the bladder wall (transmural inflammation) and surrounding nerves (perineuritis)

L: Bladder lumen, bar: 500  $\mu$ m

## Discussion

Chronic ketamine abuse commonly manifests as lower urinary tract symptoms, pelvic pain, and decreased bladder capacity.

A proportion of these patients develop vesicoureteral reflux and hydronephrosis as a consequence of the small capacity and rise in pressure in the severely contracted fibrotic bladder (4,16).

**Table 1. Clinical features of ketamine-induced uropathy (4-12)**

|   |  |
|---|--|
| <b>Common presenting symptoms</b>   |  |
| Urinary frequency   |  |
| Urgency   |  |
| Dysuria and/or hematuria  |  |
| Pyuria  |  |
| Nocturia  |  |
| Urge incontinence   |  |
| Small bladder capacity  |  |
| Postmicturition pelvic pain-lower abdominal pain  |  |
| Acute pyelonephritis  |  |
| <b>Technical findings (cystoscopy, video-urodynamic studies, ultrasound, computed tomography)</b> |  |
| Urothelial inflammation with or without ulceration  |  |
| Mucosal tearing   |  |
| Hypervascularity, neovascularization, glomerulation, and petechial hemorrhages                    |  |
| Easy mucosal bleeding   |  |
| Thickening of the bladder wall  |  |
| Detrusor overactivity and/or decreased bladder compliance   |  |
| Decreased bladder capacity  |  |
| Vesicoureteral reflux   |  |
| Ureteral stenosis/strictures – “walking-stick or hockey-stick ureters”                            |  |
| Hydronephrosis  |  |
| Renal impairment  |  |
| Papillary necrosis  |  |

**Table 2. Overview of the histological features of ketamine-induced uropathy**

| Tissue         |   | References  |   |
|----------------|---|---|---|
| <b>BLADDER</b> | <b>Epithelium</b>   | Denudation of the urothelium ± reactive changes/cellular atypia (mimicking carcinoma <i>in situ</i> )   | (4,13)                                    |
|                |   | Supra-basal expansion of nerve growth factor receptor expression  | (14)                                      |
|                | <b>Stroma (lamina propria ± submucosa)</b>  | Edema of the lamina propria   | (9)                                       |
|                |   | Inflammatory infiltrate (can consist of neutrophils, lymphocytes, plasma cells, and variable numbers of eosinophils occasionally present)   | (4,6)                                     |
|                |   | Accumulation of intravascular eosinophils   | (9)                                       |
|                |   | Proliferative/reactive changes in von Brunn nests with cystic dilatation (cystitis cystica) and glandular metaplasia (cystitis glandularis)   | (12)                                      |
|                |   | Mast cell infiltration (mastocytosis)   | (6)                                       |
|                |   | Granulation tissue formation  | (4,6)                                     |
|                |   | Increased deposition of collagen (fibrosis)   | (9)                                       |
|                |   | Calcification   | (6,9)                                     |
|                |   | <b>Vascular changes</b>   |   |
|                |   | Increased sub-epithelial capillarization, congested vessels, Hypervascularity, neovascularization, petechial hemorrhages <sup>*</sup><br>Fibrinoid necrosis of arterioles <sup>**</sup> | <sup>*</sup> (4,8,9)<br><sup>**</sup> (6) |
|                | Neurogenesis: numerous fine neurofilament protein positive (NFP+) nerve fibers in the lamina propria, stromal nerve hyperplasia, neuroma-like lesions | (14)  |   |

**Table 2. Continued**

| Tissue                    |  | References  |       |
|---------------------------|--|---|-------|
| BLADDER                   | Muscularis   | Inflammatory infiltrate (can extend to ureters or adjacent peritoneum)                          | (4,6) |
|                           |  | Muscle cells containing peripheral vacuoles   | (4)   |
|                           |  | Muscle hypertrophy  | (6)   |
|                           |  | increased deposition/accumulation of collagen (fibrosis)<br>degeneration of smooth muscle cells | (6,9) |
|                           |  | Mast cell infiltration (mastocytosis)   | (6)   |
|                           |  | Nerve hyperplasia   | (14)  |
|                           | Inflammation around nerve bundles (perineuritis)   | PC <sup>s</sup>   |       |
| Adventitia/<br>serosa     | Transmural inflammation with adhesion of bladder to peritoneum   | (6)   |       |
| URETER                    | Edematous changes (swelling)   | (6,15)  |       |
|                           | Ureter wall thickening   | (4,6)   |       |
|                           | Inflammatory infiltrate (incl. eosinophils)  | (4,6,15)  |       |
|                           | Transmural inflammation with secondary fibrosis*<br>fibrosis and reactive changes extending into the surrounding fat tissue**  | *(4)<br>**PC <sup>s</sup>   |       |
|                           | Purulent inflammation (infiltrate of neutrophilic granulocytes) in mucosa and submucosa<br>chronic inflammation (lymphocytic infiltrate) extending into muscularis propria | PC <sup>s</sup>   |       |
|                           | Erosion of the urothelium  | (15), PC <sup>s</sup>   |       |
|                           | Nephrogenic/intestinal metaplasia  | (15)  |       |
|                           | Inflammatory polyps  | (12)  |       |
| Increased vascularization | PC <sup>s</sup>  |   |       |
| KIDNEY                    | Congested parenchyma; scattered calcifications (predominantly in medullary pyramids)<br>Interstitial inflammation (interstitial nephritis)*<br>Papillary necrosis*         | PC <sup>s</sup><br>*(11)  |       |

PC<sup>s</sup>: Present autopsy case

Patients may not readily disclose chronic ketamine abuse; therefore, in the absence of a clear explanatory cause (e.g. chemoradiation therapy or infection), the main differential diagnosis might be interstitial cystitis (or "bladder pain syndrome"). These conditions share several histological features (17), but distinctions can be found in epidemiologic characteristics (10,18), comorbidities (19), and etiology (20). Other rare etiological factors causing chronic urothelial inflammation and leading to small contracted bladders include: eosinophilic cystitis, genitourinary tuberculosis, and schistosomiasis (21).

In 2008, ureteral fibrosis was observed due to an intense inflammatory response secondary to the excretion of ketamine and its metabolites in urine (4). Meanwhile, *in vitro* and *in vivo* studies have shown that ketamine exposure exerts direct effects. Pathogenesis probably involves several connected pathways, resulting in urothelial cytotoxicity and enhancement of cell apoptosis (disrupted barrier function), inflammation with stromal neurogenesis (nerve hyperplasia), microvascular injury, and increased collagen expression (fibrosis) (9,16,22). Direct toxic effects have also been demonstrated with

ketamine's main metabolite, norketamine (NK). NK also induces urothelial apoptosis triggered by mitochondrial dysfunction and endoplasmic reticulum stress. Furthermore, NK exerted a more potent cytotoxic effect than ketamine (22).

Our findings of interstitial nephritis, papillary necrosis, and extensive transmural ureteral fibrosis illustrate that the toxic effects of chronic ketamine abuse extend beyond the bladder. Progression to end-stage bladder and ureteral involvement can occur rapidly, with a time interval of months to a year if the abuse continues (10).

The above-mentioned mechanisms of cell death, inflammation, and fibrosis could explain the ureteric strictures resulting in hydronephrosis, which are increasingly observed in our practice. The concept of "ketamine-induced uropathy (KIU or KU)" (10) is preferred over "ketamine-induced cystitis," as this acknowledges the extensive upper tract implications.

## Conclusion

This perspective encourages urologists to clearly assess the ureters before proceeding with reconstructive bladder surgery,

as hydronephrosis can stem from not only low-capacity high bladder pressure but also direct ureteral damage. This is an important fact to acknowledge because an unrecognized ureteral stricture can lead to severe kidney failure. Our findings might impact the medical treatment and prevention of uropathy as well. After all, bladder instillations with hyaluronic acid and glycosaminoglycan have been found to help restore the inner bladder lining. It is possible that recently available oral formulations may also protect the ureters.

## Ethics

**Informed Consent:** The Ethics Committee of the Antwerp University Hospital (UZA)/UAntwerpen provided a waiver of informed consent for publication of this postmortem case report, as this examination was conducted within a judicial context.

## Footnotes

### Authorship Contributions

Surgical and Medical Practices: E.B., D.D.H., W.J.M.L. D.W., G.D.W., Concept: E.B., D.W., G.D.W., Design: E.B., G.D.W., Data Collection or Processing: E.B., D.D.H., G.D.W., Analysis or Interpretation: E.B., D.D.H., M.L., G.D.W., Literature Search: E.B., G.D.W., Writing: E.B., D.D.H., W.J.M.L. D.W., G.D.W.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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