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Review article

Imaging diagnosis of ketamine-induced uropathy☆

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ABSTRACT

With growing ketamine abuse, ketamine-induced uropathy (KIU) has become a vital health issue in recent years. Although the lower urinary tract is the primary affected site, involvement of the upper urinary tract is common, and KIU may progress rapidly. The main objective of a baseline imaging study is evaluating the extent and complications of KIU after excluding other causes of uropathy. A comprehensive strategy for KIU evaluation through imaging is essential for effectively managing complications and preventing further renal function deterioration. In this study, we describe the imaging presentation of KIU and examine the role of various imaging modalities, such as ultrasound, intravenous urography, and computed tomography, in diagnosing patients with KIU.

1. Introduction

Ketamine, a rapid-onset and short-acting anesthetic introduced in the 1960s,[1] has become a recreational drug during the past 10–20 years because of its dissociative effect and addiction-inducing properties.[2] Ketamine abuse is prevalent in Taiwanese nightclubs and has become the leading cause of substance abuse in Taiwan since 2006.[3] Street ketamine abuse may lead to serious urological conditions and impose a substantial burden on health care resources. Ketamine-associated ulcerative cystitis was first reported in 2007 by Shahani et al,[4] when a patient presented with lower urinary tract symptoms, namely severe dysuria, frequency, urgency, and gross hematuria. Thereafter, ketamine-induced uropathy (KIU) has been extensively reported in the literature.[5]

The effect of ketamine on the urinary bladder is well established. Studies have postulated that high concentrations of ketamine and its metabolites in urine might have a direct toxic effect on urothelial cells, causing microvascular changes and neurogenic inflammation or evoking autoimmune responses.[2,6] Histopathological findings in experimental mice treated with ketamine revealed a loss of muscular proportion in the bladder wall accompanied with increased fibrosis, principally in the lamina propria and the muscular layer, which is clinically correlated with a contracted urinary bladder.[7] Bladder biopsies of patients with KIU typically exhibit ulceration, inflammatory cell infiltration (predominantly eosinophils), and a varying degree of fibrosis.[4,5,8] Cystoscopic examination and biopsy (predominantly eosinophilic infiltration) both suggest eosinophilic cystitis, but the absence of documented peripheral eosinophilia and eosinophilic sediment excludes this diagnosis.[5] Whether KIU represents a new type of eosinophilic cystitis is currently unclear.

KIU diagnosis is primarily established by the clinical presentation of severe lower urinary tract symptoms and a history of ketamine abuse. The typical presentation symptoms include severe urgency, urinary frequency, intermittent hematuria, nocturia, dysuria, and bladder pain.[3–5,9–11] Lower urinary tract examination, including urodynamic and cystoscopic examination, are recommended for these patients. Low bladder capacity and detrusor muscle overactivity are the usual findings of urodynamic examinations in patients with KIU.[8] Rigid cystoscopy is an important diagnostic tool in examining patients with KIU for excluding other hematuria causes and evaluating interstitial cystitis severity through visual inspection and biopsy.[5,10] Cystoscopy findings typically include a contracted bladder with reduced capacity, as well as severe inflammation and epithelial denudation, which are indicators of ulcerative cystitis.[5] However, cystoscopy has limitations. It is invasive, painful, and usually requires general anesthesia.

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Its evaluation range is limited to the urinary bladder, thus, it cannot rule out upper urinary tract involvement.

Although the lower urinary tract is the primary site affected in patients with KIU, the upper urinary tract can be equally involved.[2,9] Ketamine metabolites can be detected in the gelatinous debris aspirated from the pelvicalyceal systems and the ureter.[12] A study of ketamine addiction in mice revealed foci of mononuclear cell infiltration around the glomeruli and the blood vessels within the kidney and ureter, suggesting that ketamine induces chronic interstitial inflammation.[13] KIU incidence involving the upper urinary tract varies widely in literature and ranges from 13% to 51%.[2,9] Factors contributing to disease extent, such as dosage and frequency of ketamine abuse, and symptom severity are currently unavailable. Furthermore, a previous study reported no significant correlation between interstitial cystitis severity and the upper urinary tract involvement in KIU.[14]

KIU may progress rapidly, therefore, close monitoring and imaging modalities are necessary for analyzing renal function (Fig. 1).[14] Because low bladder capacity is the major complication of KIU, augmentation cystoplasty is usually suggested for symptom relief. However, if the patient continues ketamine abuse, the disease further progresses to the upper urinary tract. In such cases, augmentation cystoplasty cannot benefit the patient. In a study by Ng et al,[15] four patients with KIU were treated for ketamine-related bladder contractures using augmentation cystoplasty. All four patients resumed ketamine consumption after surgery. The mean maximal baseline and postoperative bladder capacity were 37.5 cc (range, 25–50 cc) and up to 400–500 cc, respectively. However,

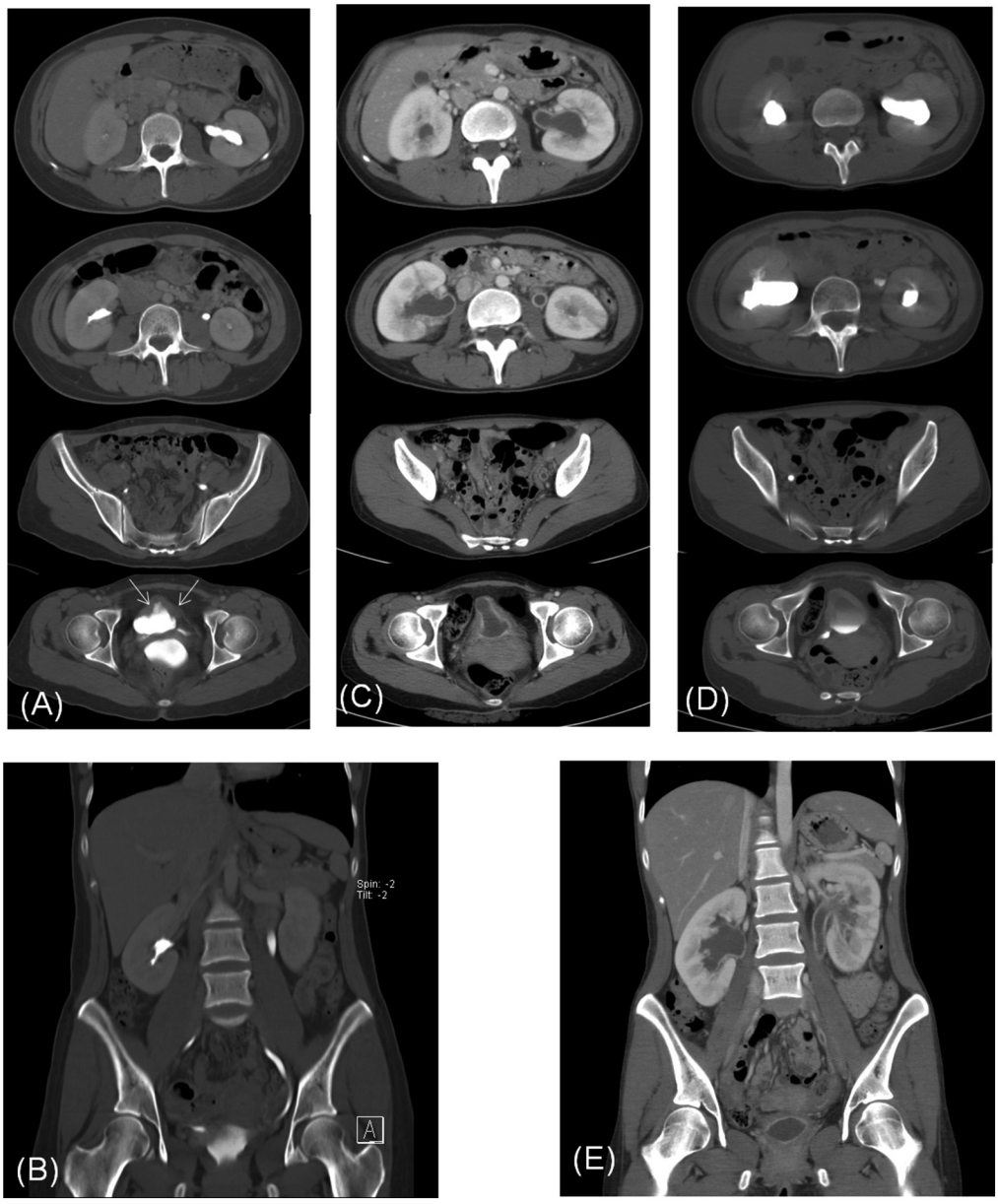

Fig. 1. CTU study of a 24-year-old woman with a 2-year history of ketamine abuse. (A) Sequential axial post-contrast images and (B) coronal reconstruction image of a split-bolus CTU study. The axial images of the combined nephrographic and excretory phase reveal bladder wall thickening (arrows) and a small bladder volume. There is no hydronephrosis or hydroureter. (C–E) Three-phase CTU exam after 6 months [(C) nephrographic phase, (D) excretory phase, and (E) coronal reconstruction of nephrogenic phase] demonstrates diffuse strong mucosal enhancement of renal pelvis and ureters (C, E), hydronephrosis, and hydroureter, indicating rapid disease progression and upper urinary tract involvement by ketamine-induced uropathy. CTU = computed tomography urography.

three patients experienced further renal function deterioration, which was secondary to new-onset ureteral strictures in two patients and to sepsis in one patient. Therefore, simple surgical management of the physical component of the contracted bladder without a complete evaluation of disease extent and ceasing ketamine use after surgery may only temporarily relieve symptoms and cause further complications in some patients.

KIU is an emerging medical condition requiring a multidisciplinary approach to treating patients. Imaging modalities are noninvasive and first-line methods in KIU diagnosis. The main objective of baseline imaging is evaluating the extent and complications of KIU and excluding other causes of uropathy.[6,14] Imaging modalities are also used in evaluating KIU progression at follow-up. Ultrasound, intravenous urography (IVU), and computed tomography (CT) are vital imaging modalities for evaluating the morphology of the renal collecting system. Diuretic renography is a nuclear-medicine method for evaluating renal function and the severity of obstructive uropathy and differentiating between obstructive and nonobstructive causes of hydronephrosis or hydroureter. Diuretic renography could be an efficient tool for follow-up. In the following paragraphs, we introduce the findings and roles of various noninvasive imaging modalities in diagnosing KIU with a focus on ultrasound, IVU, and CT.

2. Ultrasound

2.1. Ultrasound: urinary bladder

Ultrasound should be used as the primary imaging tool for examining the urinary system in patients with KIU because it is a real-time, radiation-free, portable, and less-expensive method as compared with CT and magnetic resonance imaging. Major ultrasound findings in patients with KIU are low bladder capacity with bladder wall thickening and sometimes calcification. Blood clots may be observed in patients with hematuria. Bladder distention is recommended for accurate measurement of bladder wall thickness and volume. However, distention is usually painful for patients and can lead to detrusor muscle overactivity. In a study by Mason et al,[9] 67% of patients with ketamine-induced cystitis exhibited bladder wall thickening and low bladder volume. However, one-third (4 out of 12) of the patients were unable to fill their bladders for the examination because of extreme discomfort, and the examination was halted so that the patients could empty their bladder. Therefore, KIU diagnosis through bladder wall thickness measurement is highly controversial. Another way to measure bladder capacity is by adding the voided volume and the residual urine volume. According to the report by Tam et al,[16] patients were asked to drink as much as they could tolerate and instructed to void in the uroflowmeter when they had a strong desire to void. The urology nurse performed the ultrasound bladder scan to estimate the residual urine volume in the bladder immediately after the uroflowmetry test. Bladder emptying efficiency could be estimated by dividing the voided volume by the bladder capacity and expressing as a percentage. Since ineffective bladder emptying is another feature of KIU, both bladder capacity and voiding efficiency could be obtained by this method and, thus, could be used to evaluate the progress of, and response to, treatment for these patients.

2.2. Ultrasound: kidneys

Examining bilateral kidneys is an essential part of ultrasound exams for patients with KIU. An advantage of ultrasound is its ability to detect hydronephrosis. Huang et al[14] reported that 44.4% of patients with KIU exhibited hydronephrosis, which is consistent with the findings of Chu et al[2] (51%). Hydronephrosis in patients with KIU may be secondary to low bladder capacity, vesicle-ureteral reflux (VUR), KIU involvement in the upper urinary tract, or other causes of obstructive uropathy, such as stones or tumors. Treatment efficiency can only be determined when the cause of hydronephrosis and extent of involvement are accurately delineated. Voiding cystourethrography should be arranged to evaluate the possibility of VUR. If obstructive uropathy is observed, urine diversion through ureteral stenting or nephrostomy is necessary for relieving obstructions and early renal function preservation. In a study by Tam et al[16], renal impairment was higher in patients with hydronephrosis (4 of 13, 30.8%) than in those without hydronephrosis (6 of 147, 4.1%; $p = 0.004$).

The limitation of ultrasound is that the ureters are usually obscured on scans by bowel gas and pelvic bony structures. Ureteral thickening and luminal narrowing, which are presentations of upper urinary tract involvement, cannot be directly detected through ultrasound. Therefore, when upper urinary tract involvement is suspected, IVU and CT should be performed.

3. IVU

The entire upper and lower urinary tract can be imaged using IVU. Bilateral renal function can be compared and evaluated through sequential filming after intravenous contrast administration. When the upper urinary tract is involved in KIU, hydronephrosis and hydroureter is observed, along with luminal narrowing of the involved segment. However, IVU has some limitations. First, in cases of severe obstruction or renal function impairment, the level and cause of obstruction cannot be imaged. Second, hydronephrosis can be caused by long-term decrease in bladder compliance, VUR, KIU involvement in the ureterovesical junction, KIU involvement in the ureter, or other causes of obstructive uropathy. When the obstruction is at the ureterovesical junction, the root cause of hydronephrosis cannot be determined and distinguished from the various causes. In a study by Chu et al[2], most patients with KIU had bilateral hydronephrosis and hydroureters at the ureterovesical junctions on IVU study. Third, IVU is time consuming, which may cause uneasiness in patients with lower urinary tract symptoms.[9]

4. CT

4.1. CT techniques

Of the various imaging tools, CT urography (CTU) is the most useful because it allows simultaneous visualization of both the upper and lower urinary tracts and the ureters can be directly observed.[5,9,14] CTU is widely used in examining patients with urinary tract symptoms, particularly in hematuria diagnosis. Conventionally, the three-phase CTU comprises the noncontrast phase, the nephrographic phase, in which the scan is obtained 90 seconds after intravenous administration of the contrast medium, and the excretory phase, in which the scan is obtained at least 5 minutes after injecting the contrast medium.[17,18] Coronal multiplanar reformation images can be generated using a multislice volumetric dataset of both phases. In patients with KIU, mucosal enhancement and wall thickening can be observed clearly in the nephrographic phase, whereas the lumen of the urinary tract, particularly the ureter, can be observed clearly in the excretory phase (Fig. 1). The extent of upper urinary tract involvement can thus be determined. Excretory phase is essential for detecting congenital anomaly of the collecting system, such as duplication (Fig. 2).

Split-bolus CTU has been introduced after recent concerns regarding radiation dosage. In split-bolus CTU, 30 mL of contrast medium is administered after acquiring an unenhanced scan from the kidney to the bladder. During the interval, the patient is

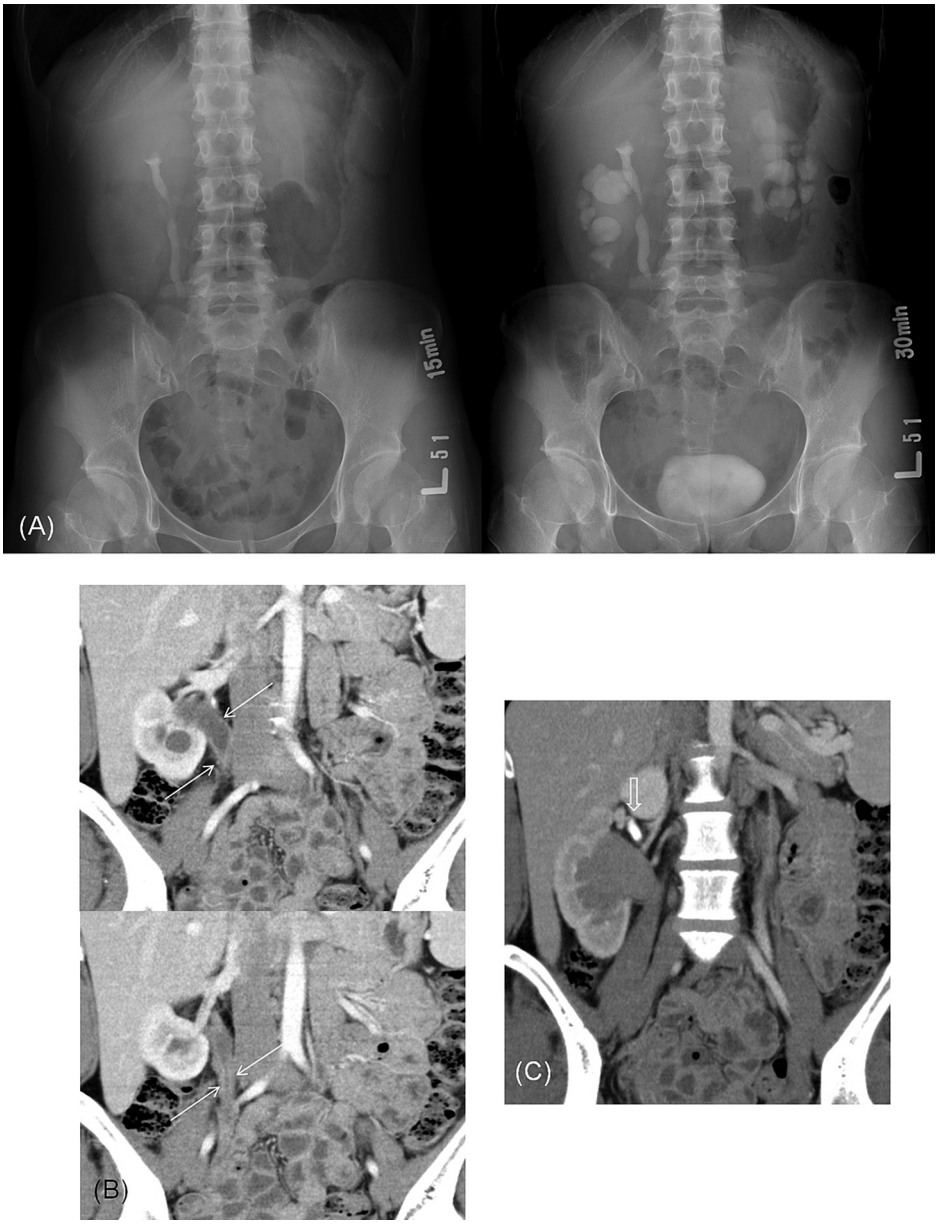

Fig. 2. A 26-year-old woman with a 2-year history of ketamine abuse, observed to have hydronephrosis and suspected to have ureteral involvement of KIU. (A) IVU study (left, 15-minute film; right, 30-minute film) reveals duplication of the right kidney. Only the collecting system of the upper moiety is opacified. The lower moiety of the right and left kidneys shows delayed function and hydronephrosis, while the obstruction level and cause could not be decided. (B, C) The coronal reformation images of three-phase CTU exam [(B) nephrographic phase and (C) excretory phase] reveals diffuse thickening of the wall of the lower moiety of the right collecting system (arrows in B) and dilatation, indicating KIU involvement. In excretory phase, the uninvolved upper moiety is opacified (open arrow in C). Note the unsymmetrical renal function of the upper and lower moiety of the right kidney. CTU = computed tomography urography; IVU = intravenous urography; KIU = ketamine-induced uropathy.

encouraged to change position or walk. After a 15-minute interval, the patient is prepared for another scan; 70 mL of contrast medium is administered and the second scan is performed for the same scan range after a 90-second interval. Coronal multiplanar reformation images can be generated using a multislice volumetric dataset of both phases. By administrating two separate boluses of contrast medium before the scan, tissue perfusion information and luminal contrast can be obtained in a single scan. The radiation dose can be effectively reduced without compromising lesion detection in the urinary tract.[18–22] Split-bolus CTU has been adapted as a standard protocol in numerous institutions and is particularly recommended for young patients.

The major concern regarding the use of split-bolus CTU in examining patients with KIU is that the mucosal enhancement is obscured by the intraluminal contrast medium. In our previous study, the segment of mucosal enhancement is observed in the nephrographic phase, and wall thickening and dilatation of the proximal ureter are invariably observed in the corresponding segment in the excretory phase.[12] Therefore, the absence of information regarding mucosal enhancement does not interfere with the ability of split-bolus CTU to determine the extent of KIU-induced inflammation.

4.2. CT features

Diffuse bladder wall thickening, low bladder volume, and perivesical infiltration are predominant CT findings (Fig. 1). When the ureter is involved, ureteral wall thickening, strong mucosal

enhancement, and dilatation of the involved and proximal urinary tract can be observed (Figs. 1 and 2). Furthermore, hydronephrosis in patients with KIU may be caused by long-term decrease in bladder compliance, VUR, KIU involvement in ureterovesicle junction, or KIU involvement in the ureter. The advantage of CT is that it demonstrates the level of ureteral involvement and excludes other causes of obstruction, such as tumors or stones. The presence of contrast medium in the vagina is not uncommon and is possibly caused by urine leakage during the examination and subsequent reflux to the vagina. The possibility of vesico-vaginal fistula should be ruled out after careful clinical history correlation and cystoscopic examination.

Radiation dose is the major concern in performing CT scans in patients with a history of ketamine abuse, as the patients are usually young. As KIU progresses rapidly, the patients may need close follow-up through imaging modalities. Alternatively, IVU and CT may be more favorable than other tests for adequate follow-up of these patients.

5. Conclusion

With growing and widespread recreational ketamine use, KIU has become a prevalent health issue in our society. The main objective of a baseline imaging study is evaluating the extent and complications of KIU and excluding other causes for uropathy. Adequate baseline imaging evaluation of KIU is key in effectively managing complications and preventing further renal function deterioration. An integrated multidisciplinary approach involving radiology, urology, psychiatry, and social services is crucial in treating these patients.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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