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CASE REPORT

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Non-oliguric acute renal failure secondary to a potentially lethal dose of caffeine with acute intoxication: a case report

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Abstract

Background Recently, the incidence of caffeine intoxication has been on an upward trend, with severe outcomes. However, acute kidney injury (AKI) resulting from renal pathologies secondary to caffeine intoxication is rare, and the pathophysiological mechanisms underlying AKI are unclear.

Case presentation A female patient in her 20s ingested an over-the-counter drug containing caffeine. The patient was diagnosed with secondary non oliguric AKI caused by acute intoxication due to ingestion of a lethal dose of caffeine. On day 19 of hospitalization, a renal biopsy was performed to determine the etiology of her prolonged renal dysfunction. Light microscopy revealed normal glomeruli, mild inflammatory cell infiltration, and acute tubular damage. Myoglobin staining was positive within the tubules, with scattered myoglobin columns. Electron microscopy revealed loss of glomerular epithelial foot processes and inflated tubular mitochondria. After undergoing hemodialysis and continuous hemodiafiltration, the patient's overall condition stabilized. After a consultation with a psychiatrist, on her 34th day of hospitalization, she was discharged home.

Conclusions Caffeine antagonizes adenosine receptors, stimulates ryanodine receptors, and elevates catecholamines. The onset of AKI is hypothesized to result from a combination of these mechanisms, resulting in tubular ischemia and injury, as well as renal artery constriction. The development of AKI was thought to be caused by the following factors: (1) disruption of the tubular oxygen supply-demand ratio and consequent ischemia due to adenosine receptor antagonism by caffeine, (2) tubular damage due to rhabdomyolysis and consequent ryanodine receptor stimulation, and (3) increased catecholamine levels and consequent renal artery constriction.

Keywords Acute caffeine intoxication, Acute kidney injury, Renal biopsy

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Background

Energy drinks and non-drowsy medications are relatively inexpensive and readily available. As the market for these drugs has expanded, cases of suicidal attempts by consuming large quantities of caffeine have resulted in successful subsequent suicides [1]. Some countries are concerned regarding the increase in caffeine addiction, enacting laws restricting the amount of caffeine purchased [2].

Acute kidney injury (AKI) resulting from renal pathologies secondary to caffeine intoxication is rare. Therefore, we investigated the pathophysiological mechanisms underlying AKI and the manifestations thereof, by presenting a near-fatal, novel case of non-oliguric acute renal failure from myoglobinuria secondary to acute caffeine intoxication. Furthermore, the underlying etiologies were elucidated from a renal biopsy.

Case presentation

A female patient, in her twenties did not have a pertinent past medical history. She was an occasional drinker and nonsmoker and was taking low-dose birth-control pills. The patient did not engage in any exertional activities in her daily life and had not performed any significant physical exercise, aside from walking and climbing stairs, in the two weeks preceding the incident.

She ingested an over-the-counter drug containing 9.8 g of caffeine, as a suicidal attempt.

Seven hours post-ingestion, she experienced dyspnea and was brought to our hospital. She was conscious, however was fairly agitated. Her initial vital signs were as follows: body temperature 36.5℃, blood pressure, 140/69 mm Hg; heart rate (HR), 230 beats/min (bpm), and respiratory rate, 24 breaths/min. Physical examination revealed pronounced, generalized sweating. Electrocardiography revealed a sustained ventricular tachycardia of 243 bpm. An arterial blood gas analysis revealed the pH, 7.32; CO2, 20.8 mmHg; HCO3, 10.6 mmHg; and lactate (Lac), 13.43 mmol/L. A urinalysis showed protein (2+) with a urinary protein level of 8.61 g/g/Cr. Laboratory results were as follows: leukocytes, 27,000/μL; creatine kinase (CK), 31,446 U/L; myoglobin, 7,000 ng/mL; creatinine (Cr), 1.04 mg/dL; potassium (K), 2.9 mmol/L; and C-reactive protein (CRP), 1.03 mg/dL. Additionally, the adrenaline, noradrenaline, and dopamine levels were 8510 pg/mL (reference range: 0–100 pg/mL), 15 910 pg/mL (reference range: 100–500 pg/mL), and 1558 pg/mL (reference range: 0–30 pg/mL), respectively.

Abdominal ultrasonography revealed an increased cortical brightness of both kidneys, short-axis swelling, consistent with AKI. Echocardiography revealed a low ejection fraction (EF) of 18%, with a pattern of generalized hypokinesis in wall motion. The discovery of a large emptied package resulted in the primary diagnosis of acute caffeine intoxication.

On admission, the patient received lactated Ringer's solution with 20 mEq of potassium chloride added, infused at 500 ml/h, and β-blockers were concurrently used to manage the tachycardia. Although the heart rate improved to 120 bpm, concerns remained regarding the ingestion of a near-lethal dose and the potential for life-threatening arrhythmias. Additionally, decreased cardiac function, suspected to be secondary to catecholamine-induced cardiomyopathy, posed a high risk of hemodynamic instability. Therefore, emergency veno-venous HD was initiated to remove both caffeine and catecholamines. Considering the possibility of exacerbating hypokalemia during hemodialysis, high-concentration KCL (KCL 20 mEq/20 ml mixed with 5% glucose 20 ml, administered at a rate of 20 ml/h) was administered concurrently during dialysis, with careful attention to prevent further progression of hypokalemia. The patient experienced pulseless electrical activity shortly before the completion of HD. After 5 min of chest compressions, intubation, and adrenaline administration, she was successfully resuscitated. Continuous hemodiafiltration (CHDF) was promptly initiated, resulting in the gradual improvement of the HR, metabolic acidosis, and levels of consciousness. On the fifth day of hospitalization, she was extubated and CHDF was terminated. The Cr levels were on an ascending trend, resulting in the re-administration of HD, on two occasions. By the 20th day of hospitalization, the Cr levels had improved to within the standard reference range. The CK level peaked at 158 500 U/L on the third day, however, gradually decreased to lie within the reference range by the 12th day of hospitalization. The levels of catecholamines were considerably elevated on presentation, which remained until the seventh day of hospitalization. Conversely, the urinary β2-microgroblin remained markedly elevated from admission until the 15th day of hospitalization. Urine protein levels were also monitored regularly through timed urine collections, revealing persistent proteinuria with levels of 0.87 g/day on day 9 and 0.68 g/day on day 15. On the 19th day of hospitalization, a renal biopsy was performed to investigate the etiology of the prolonged renal dysfunction (Fig. 1). Ten glomeruli didn't reveal any significant finding. Notably, focal, inflammatory cell infiltration within the interstitium, in addition to tubular epithelium denaturation and detachment from the basement membrane were observed. Myoglobin staining revealed the presence of stained tubules and scattered myoglobin columns. Fluorescence staining yielded negative results. Electron microscopy revealed a mild loss of the epithelial foot processes of the glomeruli. The mitochondria in the proximal tubular cells exhibited uniform distension with obscure cristae. Echocardiography was

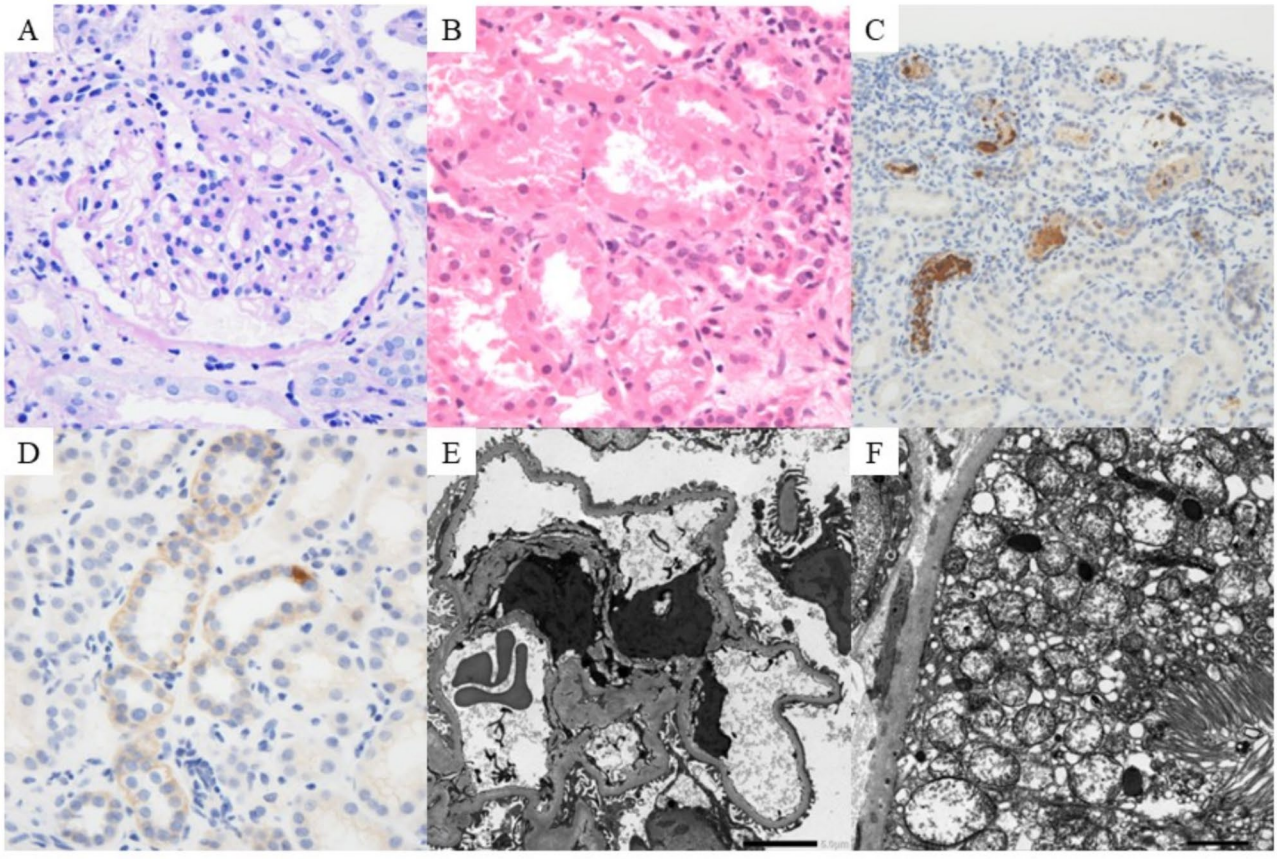

Fig. 1 Renal biopsy findings are depicted. (**A**) Periodic acid–Schiff histological staining does not reveal any substantial findings of the glomerulus (400x magnification). (**B**) Focal inflammatory cell infiltration within the interstitium, denaturation of tubular epithelium, and detachment of tubular epithelium from the basement membrane are observed on hematoxylin and eosin staining (400x magnification). (**C**)(**D**) These two images reveal the positive findings of myoglobin within the renal tubules, with the presence of myoglobin casts on myoglobin staining. (**C**) 200x magnification and (**D**) 400x magnification. (**E**) This image depicts the mild loss of epithelial foot processes in the glomerulus, by electron microscopy (12 00x magnification). (**F**) The mitochondria of the proximal tubules exhibit uniform distension, with obscure cristae, by electron microscopy (25 00x magnification)

also monitored regularly. On the day of admission, the EF was 18% with a pattern of generalized hypokinesis in wall motion, but it showed gradual improvement to 46.1% on day 3, 52.4% on day 11, and 50.8% on day 18, eventually reaching the normal range at 65.7% on day 25. The patient's overall condition stabilized. After a consultation with a psychiatrist, on her 34th day of hospitalization, she was discharged home.

The caffeine concentration was subsequently assessed using liquid chromatography–tandem mass spectrometry. Pre-dialysis, the concentration measured 24.1 μg/mL, a value within the toxic range. After 4 h of HD and subsequent CHDF, the concentration first decreased slightly and then notably to 19.4 μg/mL and 0.69 μg/mL, respectively.

Discussion

Caffeine, or 1,3,7-trimethylxanthine is a natural alkaloid commonly found in substances, including tea, coffee, and chocolate; as well as in over-the-counter medications, such as cold remedies [1]. The toxic dose of caffeine is 1–3 g, while the lethal dose is approximately 150–200 mg/kg [3]. Ideally, this patient should have undergone screening for other toxic substances. However, the emergency medical team reported that only empty caffeine tablet packages were scattered in the room. Given that the patient was alert and stated that she had taken the caffeine tablets with water and had not ingested any other substances, this account was considered credible. The over-the-counter caffeine tablets contained 100 mg of anhydrous caffeine per tablet, and the patient ingested 98 tablets, resulting in a total intake of 9.8 g, or 198.4 mg/kg, which is considered a lethal dose. The tablets also contained 5 mg of thiamine nitrate, carmellose calcium, colloidal silicon dioxide, cellulose, hydroxypropyl cellulose, hypromellose, macrogol, magnesium stearate, talc, caramel, and erythrosine as excipients. A review of safety data from the Japan Pharmaceutical Excipients Council (JPEC) revealed no reports of renal toxicity associated with these excipients in animal studies, and they were

not considered the cause of the renal injury in this case. Based on the presence of tachycardia, rhabdomyolysis, and other clinical data, the renal injury was attributed to caffeine intoxication.

The diverse symptoms of caffeine intoxication are attributable to the varying effects of certain receptors, dependent on the serum caffeine concentration. Adenosine receptor antagonism, phosphodiesterase (PDE) inhibition, gamma-aminobutyric acid (GABA) receptor suppression, and ryanodine receptor stimulation are the main underlying mechanisms [4].

Adenosine receptor antagonism, which causes gastrointestinal symptoms, headaches, and dizziness manifests at low caffeine concentrations. As the caffeine concentration increases, PDE inhibition can result in ventricular fibrillation. Simultaneously, GABA receptor inhibition results in central nervous system symptoms, including convulsions. Ryanodine receptor stimulation induces metabolic acidosis and rhabdomyolysis [4]. Moreover, severe caffeine intoxication is associated with AKI. A prospective cohort study reported that the risk of AKI was 11% lower in the group that consumed coffee regularly compared to the non-consumption group, which may seem contradictory. It is suggested that small amounts of bioactive compounds and caffeine found in coffee may inhibit the expression of Na/K-ATPase and Na/H exchanger isoform 3, thereby reducing renal tubular sodium reabsorption, which is the main source of renal oxygen consumption, without impairing renal plasma flow or GFR, ultimately reducing renal oxygen consumption [5]. A typical cup of coffee contains approximately 115–175 mg of caffeine, which is significantly lower than the toxic dose of 1–3 g, and only stimulates adenosine A1 and A2a receptors by about 20%. Therefore, the effects of caffeine are dose-dependent, with small amounts potentially offering protection against kidney injury, whereas excessive consumption at toxic levels may induce kidney damage. Three primary mechanisms underlie renal dysfunction induced by caffeine intoxication: adenosine receptor antagonism, ryanodine receptor stimulation, and catecholamine increase (Fig. 2). Adenosine exerts its effects through four receptors: A1, A2A, A2B, and A3, which are expressed in the kidneys [6]. Adenosine considerably affects the regulation of glomerular hemodynamics, by contracting and dilating the afferent and efferent arterioles, via A1 and A2 receptor activation, respectively. Additionally, adenosine possesses potent endogenous anti-inflammatory properties, potentially inhibiting inflammatory cell infiltration, endothelial adhesion, and superoxide production, via A2A receptor activation [7]. Through A2B receptor activation, anti-inflammation occurs, by suppressing the proliferation of macrophages and reducing the activation of nuclear factor kappa B [7, 8]. Adenosine may stabilize the oxygen demand-to-supply ratio, in response to the metabolic state of the kidney [6].

Caffeine is an adenosine receptor antagonist, causing the dilation and constriction of afferent and efferent arterioles, respectively. Thus, proteinuria occurs, due to elevated intraglomerular pressure. Caffeine attenuates the anti-inflammatory effects of adenosine, exacerbates glomerular and interstitial inflammation, and triggers

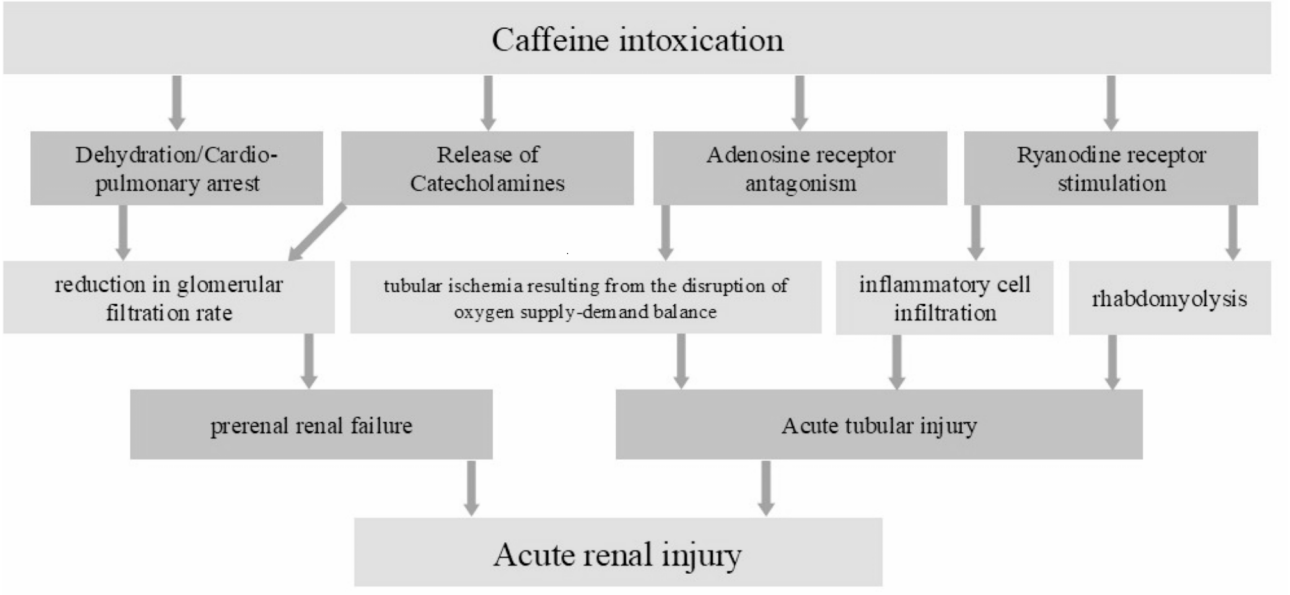

Fig. 2 The underlying mechanisms of acute kidney injury of the present case are depicted. (**1**) Dehydration, cardiopulmonary arrest, and elevated levels of catecholamines have reduced the glomerular filtration rate. (**2**) Perturbation of the tubular oxygen demand-to-supply ratio with ensuing ischemia occurs, due to adenosine receptor antagonism. (**3**) Tubular impairment arises from rhabdomyolysis, consequent to ryanodine receptor stimulation

fibrosis [7]. Furthermore, an imbalance in the oxygen demand-to-supply ratio may directly injure the tubular epithelium.

In this case, focal infiltration of inflammatory cells was observed in the interstitium. Degeneration of the tubular epithelium and detachment of the tubular basement membrane indicated tubular injury. Electron microscopy revealed proximal tubules with swollen mitochondria; however, mitochondrial injury due to AKI can result from various etiologies [9]. Tubular ischemia occurred quite considerably, because of a disruption in the oxygen demand-to-supply ratio, induced by caffeine.

Ryanodine receptors stimulation induces skeletal and cardiac muscular contraction [10]. Via this receptor, excessive caffeine intake causes an excessive contractile response within the skeletal muscles, ultimately culminating in rhabdomyolysis. A condition with symptoms strikingly similar to caffeine intoxication, including rhabdomyolysis, renal failure, tachycardia, sweating, tremors, and metabolic acidosis, is malignant hyperthermia (MH). MH is a rare disorder that typically occurs during general anesthesia, mainly triggered by the combination of inhalational anesthetics and depolarizing muscle relaxants. This condition is caused by mutations in the ryanodine receptor type 1 gene, which encodes a calcium release channel in skeletal muscle, leading to excessive calcium release from the sarcoplasmic reticulum within muscle cells and subsequent muscle hypercontraction [11]. Similar to the mechanism of rhabdomyolysis observed in MH due to ryanodine receptor type 1 mutations, it is suggested that caffeine intoxication can also cause rhabdomyolysis and associated renal failure through ryanodine receptor stimulation. In MH, muscle rigidity, including trismus, occurs, along with the generation of significant heat, leading to hyperthermia. This indicates that calcium release from the sarcoplasmic reticulum is more pronounced in MH than in caffeine intoxication. AKI secondary to rhabdomyolysis stems from multiple mechanisms, including renal vasoconstriction-induced ischemia, myoglobin-induced tubular toxicity; and obstruction of the distal tubules, by the Tamm–Horsfall protein and myoglobin complex [12]. In this case, the CK levels surpassed 150 000 U/L, on the third day of hospitalization. A renal biopsy revealed myoglobin-stained distal tubules with scattered myoglobin columns. These findings suggest that tubular injury resulted from a direct consequence of adenosine receptor antagonism and an indirect outcome of ryanodine receptor stimulation.

Furthermore, caffeine can elevate catecholamine release, by affecting the adenosine A1 receptor and adrenal medulla [13]. Notably, substantial quantities of catecholamines cause the constriction of afferent arterioles and a reduction in the glomerular filtration rate [14]. Additionally, renin secretion is induced, activating the renin-angiotensin-aldosterone system (RAAS), thus intensifying vasoconstriction [14]. This could be attributed to the potent catecholamine-induced vasoconstriction and RAAS activation, outweighing any potential vasodilation due to adenosine receptor antagonism. The extent of these effects is relatively dependent on caffeine concentration; nonetheless, post-mortem investigations of those who succumbed to caffeine intoxication have revealed higher caffeine concentrations in the kidneys than that in other organs [15, 16]. Thus, the effects of caffeine are more pronounced in the kidneys than that in other organs. Furthermore, caffeine is relatively inexpensive and can be easily purchased without a doctor's consultation or prescription; however, as this case suggests, it has the potential to cause severe renal dysfunction. Therefore, manufacturers of caffeine-based products should emphasize warnings regarding the risk of kidney injury from excessive consumption.

In conclusion, we report a case of AKI diagnosed as a result of potentially lethal caffeine intoxication. Together with the results of a renal biopsy, several pathophysiologic mechanisms of AKI due to caffeine intoxication were considered.

Abbreviations

AKI	Acute kidney injury
bpm	Beats/min
CHDF	Continuous hemodiafiltration
CK	Creatine kinase
Cr	Creatinine
CRP	C-reactive protein
EF	Ejection fraction
GABA	Gamma-aminobutyric acid
HD	Hemodialysis
HR	Heart rate
JPEC	Japan pharmaceutical excipients council
K	Potassium
Lac	Lactate
MH	Malignant hyperthermia
PDE	Phosphodiesterase
RAAS	Renin-angiotensin-aldosterone system

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Author contributions

All authors diagnosed and treated the patients. AM drafted and KI, MY and SH critically revised the manuscript. All authors read and approved the final manuscript.

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None.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. The totality of the data cannot be shared based on patient confidentiality concerns.

Declarations

Ethics approval and consent to participate
Ethical approval was not sought for the present study because a case report is a medical activity.

Consent for publication
Written informed consent for publication of the clinical details was obtained from each of the patient and a copy of each consent form is available if requested by the Editor of the journal.

Competing interests
The authors declare no competing interests.

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