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Exceptional Case

Heroin crystal nephropathy

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Abstract

In this paper we present an interesting case of acute kidney injury and severe metabolic alkalosis in a patient with a history of heavy heroin abuse. Urine microscopy showed numerous broomstick-like crystals. These crystals are also identified in light and electron microscopy. We hypothesize that heroin crystalizes in an alkaline pH, resulting in tubular obstruction and acute kidney injury. Management is mainly supportive as there is no known specific therapy for this condition. This paper highlights the utility of urine microscopy in diagnosing the etiology of acute kidney injury and proposes a novel disease called heroin crystal nephropathy.

Keywords: acute kidney injury; crystal nephropathy; heroin nephropathy; urinalysis; urine microscopy

Introduction

The chronic use of heroin has been associated with multiple renal pathologies [1]. In 1970, an association between nephrotic syndrome and chronic heroin and cocaine use was reported [2]. Henceforth, this disease has been referred to as heroin-associated nephropathy. Typically, patients present with azotemia, hematuria and nephrotic-range proteinuria [3]. Kidney biopsies of African Americans who abuse heroin showed focal segmental glomerulosclerosis as the predominant finding while membranoproliferative glomerulonephritis was the common pathologic description in affected Caucasians [4, 5]. Of note, these studies included patients concomitantly infected with either hepatitis C or human immunodeficiency virus; thus, this led some authors to postulate that the biopsy findings are the result of the viral infection rather than heroin's effect on the glomeruli. Importantly, morphine, the active metabolite of heroin, is known to have a direct cytotoxic effect on the renal parenchyma including mesangial cell and glomerular epithelial cell hyperplasia. This is thought to be mediated by activated macrophages that ultimately cause mesangial matrix synthesis and injury from oxidative stress [6–9]. Both an increased incidence of amyloidosis and rhabdomyolysis-induced acute tubular necrosis have also been described in heroin abuse [10].

Heroin production is a four-step process, which begins with extraction of raw opium from *Papaver somniferum* [11], followed by synthesis of morphine and then its acetylation into heroin. Alkalinization of heroin into its base form is achieved by the addition of bicarbonate or ammonia. The final step is the transformation of the heroin base into the salt form with the addition of hydrochloride acid and ether. This final step is critical in making heroin water-soluble for injection [12, 13]. More than twenty substances have been used as adulterants or diluents for heroin including procaine, caffeine, paracetamol, mannitol, acetic acid, quinine, dextrose, paracetamol, phenobarbital, methanol, and acetone [14, 15].

Taken intravenously, heroin bypasses first-pass metabolism in the liver where heroin is metabolized into its active form morphine glucoronides [16]. Only 20–40% of heroin is bound to albumin or erythrocytes. It has a volume of distribution of 60–100 L and a half-life of 1.3–7.8 min [17]. Micropuncture studies have shown that heroin is freely filtered, actively secreted in the proximal convoluted tubule and partly reabsorbed in the distal segments, resulting in net tubular excretion [18, 19]. This concept is important in establishing the possible causal relationships between tubular injury and heroin use. The presence of acute kidney injury also potentiates heroin toxicity.

Mainly a disease of concentration, crystal nephropathy is dependent on both the renal tubular fluid composition and substrate concentration. In addition, the deposition of crystals into the renal epithelium depends upon the integrity of the renal tubular epithelial cells [20]. Crystal deposition is more likely to occur in the presence of tubular epithelial injury. In rats, crystals do not adhere to normal epithelial cells but more easily deposit in damaged ones [21]. Acute kidney injury (AKI) results from either obstruction of the tubular lumen or direct cytotoxicity of the crystals on the renal epithelium. The former is mainly influenced by

the solubility of certain substances in the normally acidic urine [22]. Certain substances are known to crystalize in acidic urine (e.g. calcium, calcium oxalate) while others in alkaline urine (e.g. calcium phosphate, struvite, protease inhibitors and quinolones) [23–27]. Direct cytotoxicity to the renal epithelium can result from the production of inflammatory substances such as IL-1β that stimulate cytokine release and neutrophil recruitment, ultimately resulting in tissue remodeling and renal failure [28].

Existing literature on heroin crystals is exclusive to experimental microcrystalline studies used in forensic drug analysis. There is no published report of heroin crystal causing direct nephropathy. In this paper we present a possible case of acute kidney injury as a result of heroin crystal deposition in the renal tubules.

Case report

A 42-year-old male with history of untreated hepatitis C and polysubstance abuse was admitted for AKI and severe metabolic alkalosis. One day prior to admission, he admitted to having injected a massive amount of heroin and subsequently presented with nausea, vomiting and altered mental status. On presentation, his vital signs revealed a blood pressure of 120/80, heart rate of 98, respiratory rate of 10 and a temperature of 98°F. The rest of his physical exam was normal. His blood chemistry showed Na 138 meq/L, Cl 63 meq/L, HC03 more than 56 meq/L, BUN 67 mg/dL, creatinine 4 mg/dL, and normal creatinine kinase. Arterial blood gas showed pH 7.55, pCO2 82, and tC02 73 consistent with severe metabolic alkalosis and concomitant respiratory acidosis. His urine electrolytes revealed Na 40 meq/L, Cl 28 meq/L, creatinine 43 mg/dL, and osmolality 261 mOsm/kg, with a fractional excretion of sodium (FENa) of 2.72%. Urinalysis was negative for glucose, blood, protein, white blood cells or eosinophils, while the urine pH was >8. Urine microscopy showed packed crystals that resembled broomsticks without renal tubular epithelial cells or casts (Figure 1 low power and Figure 2 high power). Renal ultrasound showed two normal size echogenic kidneys without hydronephrosis or calculi.

Despite the initial fluid resuscitation with 4 L of intravenous normal saline, the patient remained oliguric with 350 mL urine output in the first 24 h of admission. Because of the lack of improvement in his serum creatinine and urine output in the first 72 h, a kidney biopsy was performed. Light microscopy revealed diffuse acute tubular injury with numerous intratubular crystals demonstrating an unusual, finely granular to 'fluffy,' deeply basophilic appearance (Figures 3 and 4). Focally, the crystals were associated with tubular rupture and interstitial inflammation. The glomeruli were unremarkable, and there was no significant interstitial fibrosis or tubular atrophy. Direct immunofluorescence microscopy was negative for immune complex deposition. Electron microscopy demonstrated occasional intratubular crystals with peripheral radiating spicules, located within tubular epithelial cells and in the tubular lumens (Figures 5 and 6).

After 5 days of continued IV saline infusion the patient's creatinine improved to 2.9 mg/dL with a urine output of 1500 mL/24 h. Repeat urinalysis showed a pH of 6.5 and significantly less crystals. The final diagnosis was severe metabolic and AKI from heroin crystal nephropathy.

Discussion

To our knowledge this is the first reported case of AKI from heroin crystallization in the renal tubules. Despite the

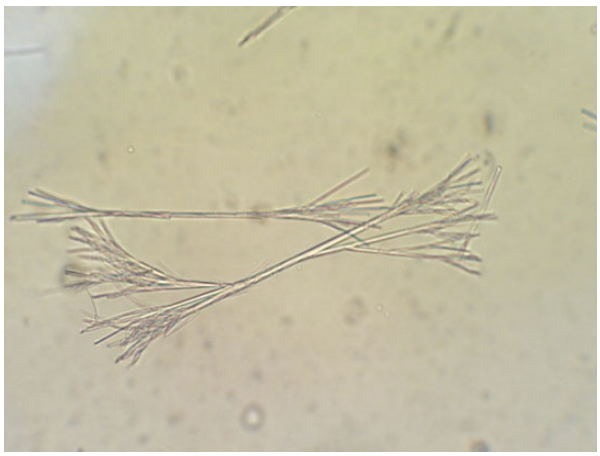

Fig. 1. Urine microscopy showing numerous crystals with broomstick-like configuration (×100).

Fig. 2. Urine crystals showing characteristic slender blades with branching threads (×400).

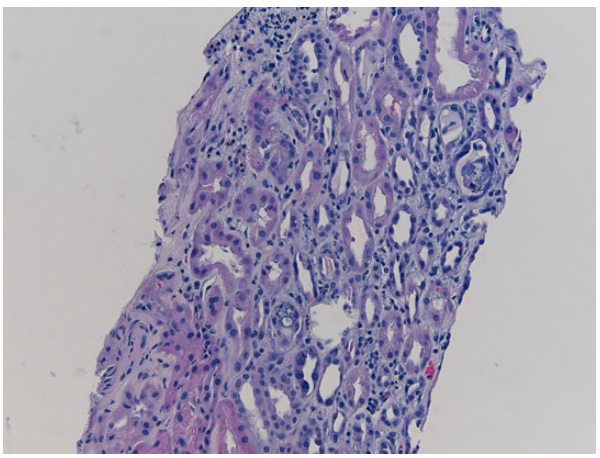

Fig. 3. Light microscopy reveals diffuse acute tubular injury with attenuation of the proximal tubular epithelial cells and frequent mitoses, focal interstitial inflammation, and numerous intratubular crystals (H&E, ×200).

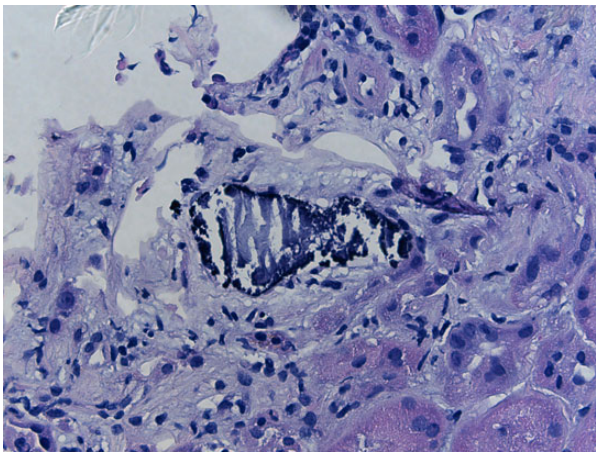

Fig. 4. Some of the crystals demonstrate an unusual, finely granular to 'fluffy,' deeply basophilic appearance (H&E, ×400).

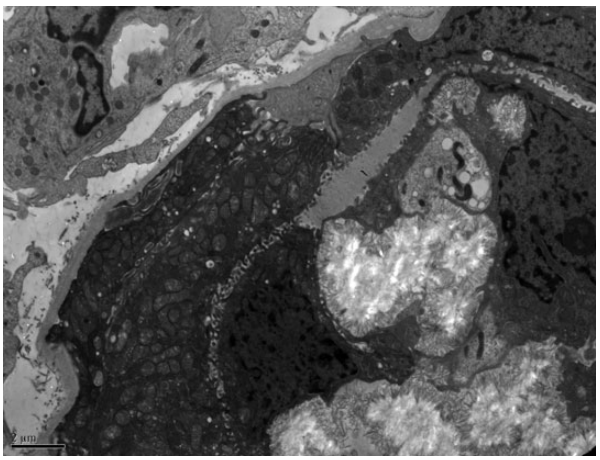

Fig. 5. Electron microscopy showing several tubules with intracellular and intraluminal crystals (×2600).

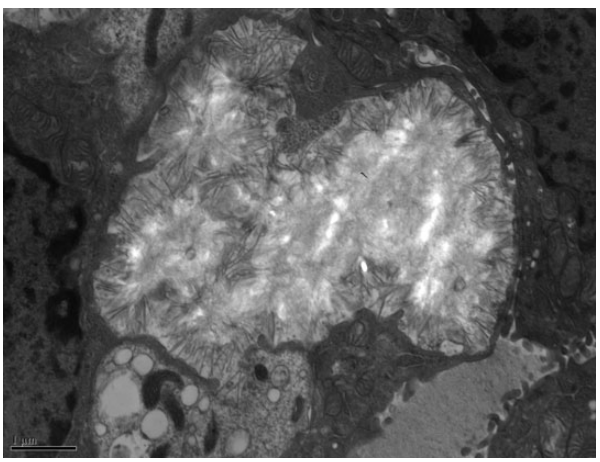

Fig. 6. Ultrastructural detail of the crystals demonstrates radiating spicules (×5800).

prevalent use of this illicit drug, there have been no reported cases of heroin crystal-related diseases. However, several experimental studies have yielded similar crystals from heroin-containing fluids. In fact, forensic drug analysis has employed microcrystalline identification technique in the detection of heroin. This test relies on the interaction of the analyte moiety with a known reagent forming a specific crystal structure [29]. Depending on the reagent used, heroin, or its metabolites, can precipitate into crystals in the forms of needles, spicules or rosettes. Specifically, when a sample is mixed with mercuric iodide in 10% HCl heroin crystallizes into characteristic slender blades with branching threads; when mixed with gold bromide in diluted sulfuric acid heroin forms fine needles that are mostly scattered; and addition of gold chloride in diluted sulfuric acid results in crystals that resemble rosettes of needles [30]. It was not noted whether it is the heroin or its metabolites that formed these crystals, but for simplicity we uniformly used the term heroin crystals in this paper. It is also possible that adulterants can influence the crystal structure identified in the microcrystalline analysis [31]. Thus with the growing number of adulterants and diluents added to the heroin salt, microcrystalline test has been largely replaced by other direct methods such as spectrometric and immunoassay studies [32]. We acknowledge the fact that the crystals that we observed could have also been from the possible adulterants in the heroin consumed by the patient. However, after our diligent background review none of the most commonly used heroin adulterants produced crystals with a morphology similar to that of our patient.

The risk factors for crystallization include supersaturated concentrations of a substance, volume depletion, reduced glomerular filtration rate and an appropriate urinary pH [33]; all of these conditions were present in our patient. Based on its pharmacokinetics, heroin is completely dissolved in the normal range of urinary pH. However, above the pH of 7.95, the ionization constant (pka), heroin's solubility decreases and it readily precipitates into crystals [34]. It is for this reason that we believe heroin crystal formation is rare under physiologic pH.

Although we were not able to directly identify the specific adulterant in this case, we theorize that an alkali (e.g. sodium bicarbonate) was used, resulting in systemic metabolic alkalosis. The urine chemistry was helpful in supporting our theory of concomitant alkali ingestion. The high urine chloride and an initial urine pH of 8 suggest a predominantly chloride-independent metabolic alkalosis. In a volume-contracted status, the urine pH is usually acidic as a result of increased fractional reabsorption of bicarbonate in the proximal tubule [35]. The increased amount of filtered bicarbonate load overwhelmed the patient's bicarbonate reabsorptive capacity resulting in bicarbonaturia and an alkaline urine pH.

The patient's AKI presumed to be from volume depletion and heroin crystal-induced tubular injury. We hypothesize that the latter played a more important role in view of the biopsy findings that showed intracellular and intraluminal crystal deposition with focally associated tubular rupture and surrounding interstitial inflammation without any evidence of glomerular injury. The normalization of the urinary pH with IV hydration paralleled the disappearance of the crystals and subsequent improvement of the patient's renal function.

The management of heroin crystal nephropathy mainly involves supportive measures in the absence of a specific therapy that will either reverse or retard the process of crystallization. Aggressive IV hydration, in the absence of volume overload, will increase tubular flow rate and hasten crystal elimination. The use of diuretics to increase tubular flow rate is debatable [36] and it is uncertain

whether dialysis will improve outcomes in the absence of classic indications for renal replacement therapy. As noted above, crystal formation is pH dependent; thus increasing the solubility of the crystal by altering the urine pH is an additional treatment option [37]. Urine alkalinization is easily achieved by the addition of citrate or bicarbonate, which is useful in cases of acidic crystals such as uric acid. In contrast, there is no evidence to suggest that urine acidification promotes better outcomes and indeed some studies have failed to show effectiveness in dissolving crystals via this approach [38, 39]. For this reason urine acidification is not a recommended treatment option for nephropathies from alkaline crystals.

This paper highlights the utility of urine microscopy, a technique that is now less commonly performed by clinicians and nephrologists, in diagnosing the etiology of acute kidney injury. Also, it proposes a novel disease. Although heroin-associated nephropathy has been described in the literature, heroin crystal nephropathy is a novel disease. The authors believe that heroin may be a potential cause of acute kidney injury through tubular crystal deposition.

Conflict of interest statement. None declared.

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