The Crystalline Nephropathies

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Crystalline nephropathies are a unique form of kidney disease characterized by the histologic finding of intrarenal crystal deposition. The intrinsic nature of some molecules and ions combined with a favorable tubular fluid physiology leads to crystal precipitation and deposition within the tubular lumens. Crystal deposition promotes kidney injury through tubular obstruction and both direct and indirect cytotoxicities. Further kidney injury develops from inflammation triggered by these crystals. From a clinical standpoint, the crystalline nephropathies are associated with abnormal urinalysis and urinary sediment findings, tubulopathies, acute kidney injury (AKI), and/or chronic kidney disease (CKD). Urine sediment examination is often helpful in alerting clinicians to the possibility of crystal-related kidney injury. The identification of crystals within the kidneys on biopsy by pathologists prompts clinicians to evaluate patients for medication-related kidney injury, dysproteinemia-related malignancies, and certain inherited disorders. This review will focus on the clinical and pathologic aspects of these 3 categories of crystalline nephropathies.

An important but somewhat under-recognized cause of kidney disease is crystalline nephropathies. This entity is characterized by the histologic finding of intrarenal crystal deposition, primarily involving the tubulointerstitium.[1] Clinically, patients present with urinary abnormalities, such as crystalluria, proteinuria, and cylinduria, whereas tubulopathies, AKI, and CKD may also develop.[1–3] The urine microscopic finding of various pathologic crystals and/or crystal-containing casts signals the possibility of crystalline nephropathy. Identification of crystals within the kidneys on biopsy is definitive for a diagnosis of crystalline nephropathy and necessitates evaluation for the underlying cause. The pathogenesis of crystal-related kidney injury is briefly reviewed followed by discussion of crystalline nephropathies of interest to clinicians and pathologists including those owing to medications, dysproteinemias, and inherited disorders. Although calcium- and uric acid-related crystalline nephropathies are common, they are not discussed.

Pathogenesis of Crystalline Nephropathies

Intrarenal crystal deposition occurs primarily owing to the high concentration of ions and molecules traversing the tubules, which enhances the likelihood for substrate supersaturation and crystal nucleation. Crystals precipitate outside and deposit within the kidneys owing to certain innate characteristics.[4] They are molecules or ions that aggregate in a symmetrical, fixed distance and form ordered 3-dimensional structures.[4] After their supersaturation and nucleation, the crystals aggregate and grow as increasing numbers of ions or molecules are added.[2] Development of injured cell membranes combined with urinary supersaturation of molecules with crystal-forming potential provides the foundation for crystal deposition.[5] Cellular surface molecules upregulated by injured cells create a local environment favorable for crystal nucleation and adhesion, which provides the nidus for further crystal growth.[5]

Crystal deposition leads to tubular obstruction and both direct and indirect crystal-related kidney injuries (Figure 1). Phagocytosed crystals destabilize lysosomes, which release their contents inducing cellular stress and autophagic cell death.[6,7] Renal tubular cell necroptosis occurs when various engulfed crystals damage lysosomes/phagolysosomes and release cathepsin-B, cleaving key regulators of the cell death pathway—RIPK3 and pseudokinase MLKL.[6,7] In addition, crystal-triggered

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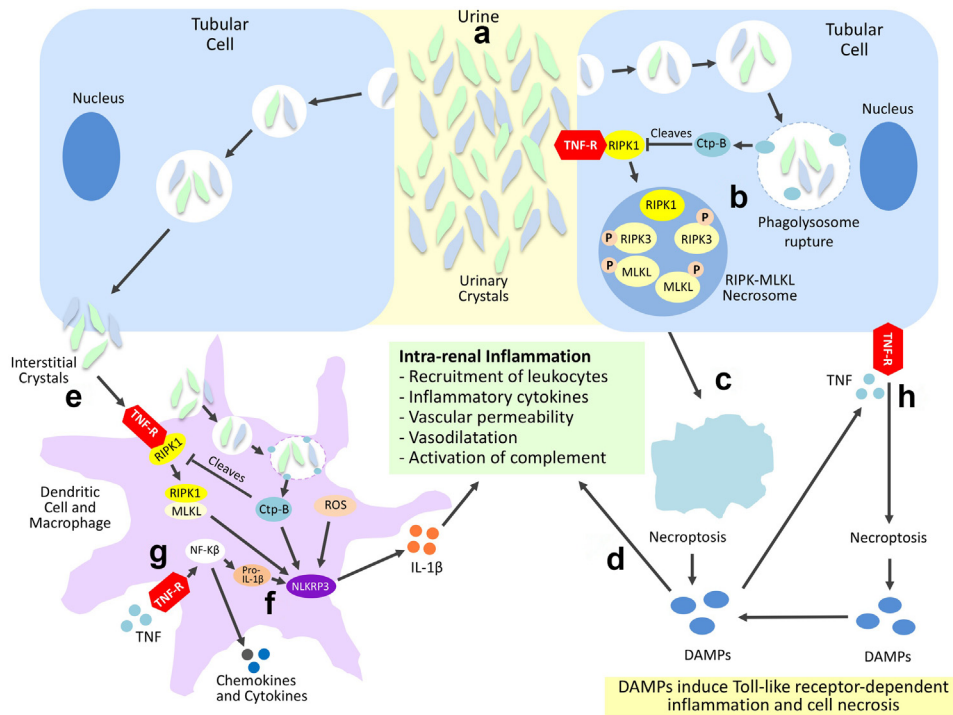
Figure 1. The mechanisms underlying crystal-related tubular cell injury and necroinflammation. Crystals precipitating in the tubular lumen (A) promote necroptosis of the tubular cells by activating a number of pathways. (B) Uptake of crystals into the lysosomes and phagolysosomes is associated with release of ctp-B when the lysosomes are destabilized. (C) ctp-B cleaves and degrades the negative regulator of necroptosis RIPK1, which triggers formation of the RIPK3–MLKL necrosome complex, which causes tubular cell necroptosis. (D) Inflammation occurs from DAMPs released from the necrosing tubular cells. (E) Dendritic cells phagocytose the crystals present in the interstitium and (F) initiate a similar process of lysosomal degradation with cat-B release and ROS formation, which activates the NLRP3 inflammasome and IL-1β secretion by the dendritic cells. (G) This leads to IL-1R–dependent inflammation in the kidney. The TNF-R pathway also activates the NF-κB, further activating the inflammasome. (H) Proinflammatory cytokines, such as TNF, trigger tubular cells necrosis by activating the TNF-R, leading to further DAMP release. Overall, these pathways promote an autoamplification loop of crystal-induced necroinflammation. ctp-B, cathepsin-B; DAMPs, damage-associated molecular patterns; IL-1R, interleukin-1 receptor; IL-1β, interleukin-1β; ROS, reactive oxygen species; TNF, tumor necrosis factor; TNF-R, tumor necrosis factor receptor.

cellular necrosis promotes the release of a number of substances into the extracellular compartment, including danger-associated molecular patterns, histones, double-stranded DNA, mitochondrial DNA, demethylated DNA and RNA, adenosine triphosphate, and uric acid.[6,7] One or more of these engage the death receptors on neighboring cells further amplifying cell necrosis.

Another important step in crystal-related kidney injury is the inflammatory process that subsequently develops. Inflammatory cell damage and necroinflammation, defined as the inflammatory response to necrotic cell death (Figure 1), promote kidney injury. Inflammatory injury within the kidneys occurs in part owing to activation of Toll-like receptors whereas complement activation and leukocyte invasion are primary effectors of harmful inflammation after crystal-related tubular cell damage.[6,7] Induction of NLRP3 inflammasome activity in kidney phagocytes and secretion of interleukin-1β, which interacts through interleukin-1 receptor, further contribute to intrarenal inflammation.[8] Tubular cell injury in a calcium oxalate crystalline nephropathy mouse model

also occurred from up-regulation of long noncoding RNA-H19 expression.[9] Up-regulated long noncoding RNA-H19 causes inflammatory injury by competitively binding microRNA-216b, which subsequently activates the danger-associated molecular pattern, high-mobility group box 1 that binds Toll-like receptor 4 and activates the NF-kB pathway. This crystal-stimulated pathway ultimately increases the transcription and expression of several proinflammatory cytokines and chemokines that induce tubular cell injury.[9–11] Cell surface lipid sorting and activation of tyrosine protein kinase Syk, which activates B-cells, is another pathway of noxious intrarenal inflammation.[6,7] Pyroptotic cell death, owing to inflammation-induced cell lysis, may also develop indirectly through crystal-related NLRP3 inflammasome production.[6,7] In addition, crystal-stimulated production of tumor necrosis factor-α and other inflammatory cytokines may promote renal tubular cell necroptosis.[6,7] All these crystal-related pathways likely contribute to injurious inflammation and cell death in the various crystalline nephropathies.

The deposition of intratubular crystals was thought to be the primary cause of AKI through induction of urinary obstruction (plugging of the tubular lumens). Acute tubular injury, often observed on the biopsy specimens, was also thought to play a contributory role in AKI. Nevertheless, robust inflammation within the tubulointerstitium generated by the crystals through the pathways reviewed previously is now thought to play a significant role in development of kidney injury. Although it is impossible to tease out exactly how much each contributes to AKI, it is likely that tubulointerstitial inflammation and tubular injury play the most important roles in causing AKI.

Medication-Induced Crystalline Nephropathies

A number of medications used in clinical practice are associated with crystalluria and crystalline nephropathy (Table 1). It is essential that clinicians and pathologists recognize the culprit drugs, their clinical presentation, and their histologic characteristics to assure proper diagnosis and treatment. Crystal deposition occurs primarily owing to the kidney route of drug/metabolite excretion and enhanced drug supersaturation within the urine. Intratubular supersaturation of drugs occurs from (i) volume depletion, which lowers urinary flow rates, and (ii) excessive drug dosing, which increases urinary drug concentrations.[1–4,12,13] Depending on the pK of the administered drug, urine pH also enhances crystal supersaturation.[1–4] Underlying acute or chronic kidney disease may further enhance the risk for medication-related crystalline nephropathy.[1–4,12,13]

Diagnosing medication-related crystalline nephropathies hinges on familiarity with culprit medications along with recognition of clinical presentation and laboratory findings, in particular urine microscopy.[4,14] It is frequent, however, for patients to be asymptomatic except for an isolated increase in serum creatinine concentration and/or abnormal urine findings. In this circumstance, pathologists play a critical role by evaluating the kidney histology to find evidence supporting crystalline nephropathy. General principles of prevention and therapy for many of these crystalline nephropathies include medication discontinuation or dose reduction, administration of i.v. fluids to restore euvolemia and enhance tubular flow rates, and modification of urine pH when appropriate. Treatment considerations specific to each form of crystalline nephropathy will be discussed for each medication.

Sulfa-Based Medications

Sulfadiazine is a sulfa-based antimicrobial agent that has been available for more than 60 years. Drug-related nephrotoxicity subsequently limited its use. Nevertheless, because it has utility for treating certain infections, clinicians should be aware of it as a cause of crystalline nephropathy.[1–4,15,16] Sulfamethoxazole, another sulfa-based antibiotic, can also cause crystalluria and crystalline nephropathy, but less frequently.[1–4] Low urinary solubility of these sulfa-drugs and their metabolites, especially in acid urine, promotes crystal precipitation within the distal tubular lumens. Furthermore, both these drugs can cause acute interstitial nephritis (AIN). When AKI occurs, it may be due to AIN, urinary obstruction from ureteral stones, or intratubular crystal deposition.

Examination of the urine sediment may reveal sulfadiazine and sulfamethoxazole crystals, which appear as free crystals or crystals within casts.[1–4,15] Crystals have hourglass shapes with prominent radial striations, also described as "sheaves or shocks of wheat" (Figure 2a), and are birefringent on polarization. Although sulfa crystals have not been observed in kidney tissue, interstitial fibrosis with mild mononuclear inflammation likely represents the effects of unseen, intrarenal crystals.[17,18] Thus, thorough urine sediment examination for sulfa-drug–related crystals and casts is important to detect crystalline nephropathy.[1,2,17] Lack of kidney recovery may signal potential AIN and require kidney biopsy for diagnosis.

Sulfadiazine- and sulfamethoxazole-associated AKIs are considered reversible. In addition to drug discontinuation when AKI occurs, i.v. fluids to increase urinary flow rates and alkaline urine achieving pH > 7.1 are useful prophylactic and therapeutic maneuvers for crystalline nephropathy to enhance kidney recovery.[1–4,17] Obstructing stones require urologic interventions along with alkaline-based i.v. fluids.

Methotrexate

Most studies note an AKI incidence, depending on population studied and AKI definition, ranging from 2% to 12% for high-dose methotrexate.[18,19] Methotrexate induces kidney injury through various mechanisms including direct cytotoxicity; however, crystal precipitation within the distal tubular lumens is likely most common.[2,4,12,13,19,20] Owing to the poor solubility of methotrexate and its metabolites, crystals tend to precipitate within the tubular lumens, particularly when decreased urinary flow rates from volume depletion, high urinary drug concentrations, and low urine pH exist.[2,4,12,13,19] Crystal-related tubular obstruction to urinary flow and generation of tubulointerstitial inflammation are the major mechanisms underlying AKI.[1–4,12,13,19]

In addition to AKI, urine sediment may reveal free methotrexate crystals and crystal-containing casts along with erythrocytes, leukocytes, and granular casts.[3,14] Crystalline cast formation (Figure 2b) in the

Table 1. Crystalline nephropathies associated with various medications

Medication	Urinary crystal morphology	Clinical renal findings	Histologic findings of the kidney	Preventive measures[a]
Sulfadiazine, sulfamethoxazole	Shocks or sheaves of wheat, shells, or dumbbells Positively birefringent on polarization	Crystalluria, nephrolithiasis, AKI, and CKD	Mild mononuclear inflammation and interstitial fibrosis noted without sulfa crystals present within tubules or interstitium	Alkalinize urine; adjust dose for kidney function; assure euvolemia before drug exposure
Methotrexate	Annular shapes, yellow, golden, or brown Positively birefringent on polarization	Crystalluria, AKI, and CKD	Annular structures consisting of small needle-shaped crystals that stain yellow, golden, or brown on H&E stain, weak rim staining on PAS, black staining on JS Positively birefringent on polarization	IVFs before/during drug, alkalinize urine, adjust drug dose for kidney function; folinic acid; glucarpidase if toxic level (<60 h after methotrexate exposure)
Indinavir, atazanavir, darunavir	Needle, rectangle, fan-shaped or starburst aggregates Positively birefringent on polarization	Crystalluria, nephrolithiasis, AKI, and CKD	Needle-shaped (translucent) indinavir, atazanavir, or darunavir crystals within tubules with an associated monocytic infiltrate and giant-cell reaction	No role for urine acidification; assure euvolemia during drug therapy; switch to different medication
Acyclovir	Thin needles with sharp or blunt ends Positively birefringent on polarization	Crystalluria, leukocyturia, AKI, and CKD	Needle-shaped crystals within tubules ± peritubular inflammation Positively birefringent on polarization	Avoid rapid i.v. bolus; adjust drug dose for kidney function; assure euvolemia during drug therapy
Triamterene	Brown, green, orange, and red spheres Positive birefringence and Maltese cross	Crystalluria, nephrolithiasis, AKI, and CKD	Crystals stain yellow/brown on H&E and PAS, silver positive on JS Strongly birefringent on polarization	Alkalinize urine; assure euvolemia during drug therapy
Ciprofloxacin, levofloxacin	Needles, stars, fans, or sheaves Positively birefringent on polarization	Crystalluria and AKI	Needle-shaped crystals within tubules Strongly birefringent on polarization	Assure euvolemia during drug therapy and avoid alkaline urine (if possible)
Amoxicillin	Thin needles, broom/brush-like Positively birefringent on polarization	Crystalluria and AKI	No histologic evidence of intrarenal deposits of amoxicillin crystals has been described on kidney biopsy findings	Assure euvolemia; adjust drug dose for kidney function
I.v. ascorbic acid, orlistat (by causing enteric hyperoxaluria), ethylene glycol	Calcium oxalate -Monohydrated: ovoid, dumbbells, or rods -Bihydrated: bipyramidal shapes Positively birefringent on polarization	Crystalluria, AKI, and CKD	Crystals are translucent to pale blue fan-like or sunburst shapes within tubules and interstitium with interstitial inflammation Positively birefringent on polarization	Ascorbic acid and orlistat: assure euvolemia during drug therapy, avoid other nephrotoxins; fomepizole ± HD for ethylene glycol
Foscarnet	Crystals as plates and geometric shapes Positively birefringent on polarization	Hematuria, proteinuria, AKI, and CKD	Plates and geometric shapes in dilated capillary loops and tubular lumens Positively birefringent on polarization	Assure euvolemia during drug therapy and adjust drug dose for kidney function
Sodium phosphate purgative (oral rather than enema)	Calcium phosphate; white, amorphous, granular structures	AKI and CKD	Granular bluish-purplish crystal deposits with positive von Kossa staining Negative birefringence on polarization	Assure euvolemia before exposure; avoid concomitant NSAIDs, diuretics, and RAS blockers

AKI, acute kidney injury; CKD, chronic kidney disease; H&E, hematoxylin and eosin; HD, hemodialysis; IVF, i.v. fluid; JS, Jones methenamine silver; NSAID, nonsteroidal anti-inflammatory drug; PAS, periodic acid–Schiff; RAS, renin-angiotensin system.
[a]Therapy includes medication discontinuation, administration of i.v. fluids for hypovolemia, and provision of supportive care, including hemodialysis.
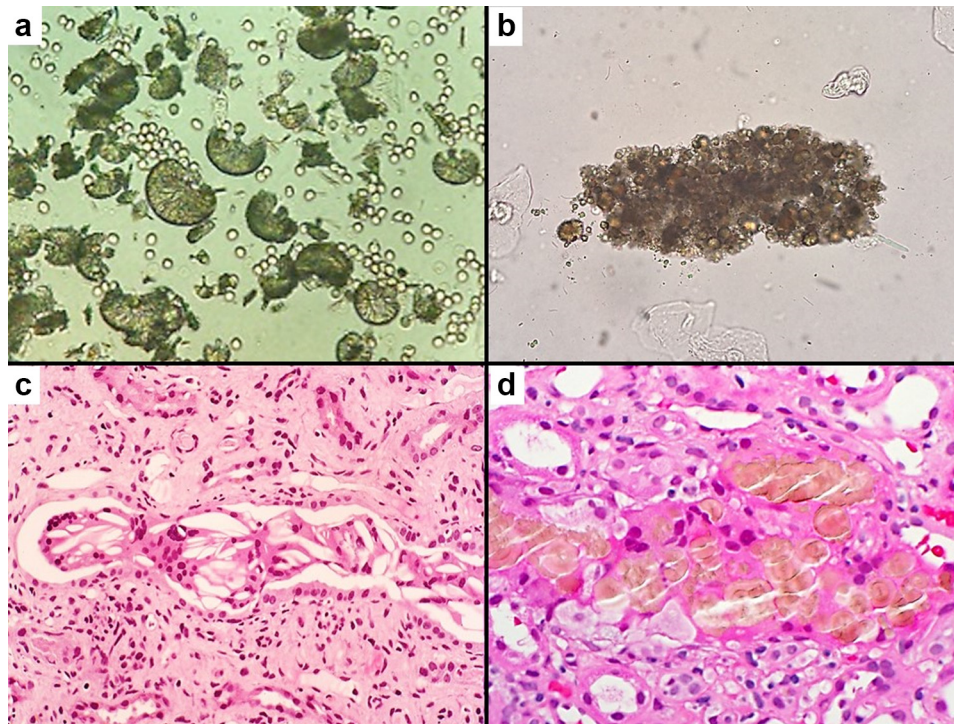
Figure 2. Various crystals found in the urine sediment results and kidney biopsy findings in patients with medication-induced crystalline nephropathies. (a) Fan-shaped sulfadiazine crystals are noted in the urine. (b) Light brown-colored methotrexate crystals are observed within a urinary cast. (c) Indinavir crystals within the tubular lumens of the kidney are found. (d) Triamterene crystals are noted within the tubular lumens of the kidney on routine H&E staining for light microscopy. Image (d) provided courtesy of Dr. Samih Nasr of the Mayo Clinic. 2D, 2-dimensional; H&E, hematoxylin and eosin.

urine suggests that precipitated methotrexate crystals caused AKI.[3] In patients undergoing kidney biopsy, methotrexate crystals form annular structures consisting of small needle-shaped crystals that stain yellow, golden, or brown on hematoxylin and eosin (H&E) stain. In contrast, the annular structures have weak rim staining on periodic acid–Schiff (PAS).[16] Silver-positive black staining of crystals is observed on Jones methenamine silver (JS), whereas strongly birefringent crystals are noted with polarization.[16]

Intratubular crystal deposition is prevented by achieving high urinary flow rates and urine alkalinization to pH > 7.[10,12,13,19,20] Folinic acid therapy after methotrexate administration provides salvage metabolic therapy. High-flux hemodialysis lowers methotrexate levels by ∼70%, but it is complicated by postdialysis rebound and the risks of dialysis catheters (bleeding, infection). Glucarpidase therapy within 48 to 60 hours of methotrexate exposure metabolizes the drug to nontoxic metabolites and effectively lowers plasma levels when AKI develops.[21] Methotrexate-associated AKI is generally reversible.

Protease Inhibitors (Indinavir, Atazanavir, and Darunavir)
Indinavir, atazanavir, and darunavir are protease inhibitors that have been used as part of combination antiretroviral therapy to treat HIV infection. Owing to their proclivity to form urinary crystals and precipitate in the distal tubular lumens, these medications are associated with crystalluria and crystalline nephropathy.[1–4,22–25] Approximately 12% of the drug is excreted unchanged in the urine, and resulting intratubular precipitation is due largely to the insolubility in the urine at pH > 3.5.[1–4,22–25] Indinavir was the first protease inhibitor associated with nephrolithiasis, crystalluria, and crystalline nephropathy.[22,23] Nevertheless, because newer protease inhibitors have replaced indinavir, focus will be on atazanavir and darunavir.

Atazanavir has been associated with postmarketing reports of crystalline nephropathy, AIN, and nephrolithiasis.[26,27] In a Japanese case-control study, patients with atazanavir-associated stones were 5 times more likely than controls to have variations in the uridine diphosphate glucuronosyltransferase-1A1 gene.[28] Whether these genetic polymorphisms also increase the risk for crystalline nephropathy is unknown. Protease inhibitor-induced crystalline nephropathy is more likely to occur in the setting of volume depletion, excessive drug dosing, low body weight, underlying liver disease, and alkaline urine.[1–4,22–27] Darunavir has also been associated with crystalluria, nephrolithiasis, and crystalline nephropathy.[24] Boosting with ritonavir

further increases the risk for darunavir-related intra-tubular crystal formation.[24] In addition to ritonavir, darunavir has similar risk factors for crystalline nephropathy and nephrolithiasis.[1–4,22–27]

Increased serum creatinine and/or abnormal urine findings reflect medication-induced kidney injury. Indinavir and atazanavir crystals in the urine appear as needle-like or rectangular shapes that can aggregate to form fan shapes or starbursts.[14,22,23,25,26] Darunavir crystals are more biconvex shaped and positively birefringent.[24] Urinary crystals may be found free or within casts, along with leukocytes and erythrocytes. Translucent, needle-shaped indinavir or atazanavir crystals clustered within the distal tubular lumens and collecting ducts with an associated monocytic inflammatory infiltrate (Figure 2c) and giant-cell reaction are observed on histologic evaluation.[1,4,18,22,25] Darunavir crystals are needle shaped or biconvex and birefringent on polarization.[24]

Nephrotoxicity is generally reversible with drug discontinuation and assuring euvolemia. There is no role for urinary acidification (pH < 4.0). Obstructing stones often require urologic intervention. Early recognition of crystalline nephropathy is critical to avoid CKD from irreversible kidney fibrosis and kidney damage.[1–4,22–27]

Acyclovir

Acyclovir is used in either i.v. or oral form to treat certain viral infections. Rapid i.v. infusion and/or high doses can cause crystalluria and crystalline nephropathy.[1–4,29] Flank discomfort and hematuria may be seen in this setting. In contrast, oral therapy and slow infusions rarely result in crystal precipitation, unless the patient is volume depleted or the dose is excessive for kidney function.[1–4,29–31] To this point, AKI may occur with excessive doses of valacyclovir and in high-risk patients.[30]

AKI or urinary abnormalities may tip the clinician off to acyclovir-related crystalline nephrotoxicity.[29–31] AIN may also rarely cause AKI. Urine sediment examination may reveal needle-shaped acyclovir crystals, which are birefringent, admixed with leukocytes or erythrocytes, or within casts.[14,29–31] In addition, biopsy result of the kidney tissue reveals needle-shaped crystals that are birefringent on polarization within the distal tubules.[4,18,29] Peritubular inflammation may also be observed.

Maintaining euvolemia and avoiding rapid i.v. infusion and high doses of acyclovir are major preventive strategies.[1–4,29] Hemodialysis is effective in removing acyclovir and may be warranted when neurotoxicity is also present. Kidney function generally recovers back to baseline in most patients.

Triamterene

Triamterene is a potassium-sparing diuretic used in combination with thiazide diuretics. Isolated crystalluria is relatively common, and both crystals and crystal-containing casts were observed in acidic urine of 20 healthy individuals administered a single 100-mg dose of triamterene.[32,33] AIN and nephrolithiasis have also been described, whereas crystalline nephropathy is relatively uncommon.[1–4,29,32,33] Triamterene undergoes hepatic metabolism; triamterene and metabolites are excreted by the kidneys.[34]

Although AKI is rare, abnormal urine sediment findings occur in approximately 50% of patients.[32,33] The urine sediment has brown-colored, round triamterene crystals and crystalline casts that are birefringent and appear as Maltese crosses.[14,29,32,33] In kidney biopsy specimens, triamterene crystals stain yellow/brown on H&E and PAS and silver positive on JS[18,33] (Figure 2d). The crystals are strongly birefringent on polarization. It is important to distinguish these crystals from 2,8-dihydroxyadenine crystals as they appear similar in urine and on kidney histology.[18,33]

Prevention of crystalline nephropathy is best accomplished by periodically monitoring serum creatinine and urine sediment, including volume depletion, nonsteroidal anti-inflammatory drug use, and acid urine, in high-risk patients. Urinary crystal and cast formation may be prevented by urine alkalinization; the treatment, however, requires triamterene discontinuation and urinary alkalinization in patients without oliguria.[1,4,18,33]

Ciprofloxacin

Ciprofloxacin is a quinolone antimicrobial agent used for various infections. Experimental studies have revealed crystalluria after use of ciprofloxacin, which is insoluble at neutral or alkaline urine pH and crystallizes in alkaline urine.[34,35] In humans, ciprofloxacin was associated with crystalluria when the urine pH was >7.3, especially when higher drug doses were used.[36] In clinical practice, ciprofloxacin-related crystalluria is unusual, developing in 2 of 63,000 patients.[37] Crystalluria was also not observed in 1556 courses of ciprofloxacin.[38] In addition, i.v. ciprofloxacin administered to 12 healthy volunteers was associated with crystalluria in 1 subject who had a urine pH of 6.3.[39]

Although ciprofloxacin has been observed to cause AIN,[40] this medication has also been noted to cause crystalline nephropathy.[41–45] Age > 70 years, alkaline urine, volume depletion, and high drug doses are risk factors for crystalline nephropathy.[41–45] Oliguric AKI develops 2 to 14 days after oral ciprofloxacin ingestion

with crystals consisting of the ciprofloxacin salt observed in the urine. Ciprofloxacin crystals appear as needles, star bursts, sheaves, fans, butterflies, and other unusual shapes.[46] Crystals have a lamellar structure and are strongly birefringent on polarization.[46] Results of kidney biopsy in 3 cases revealed needle-shaped birefringent crystals within the tubules.[44,45]

Urine sediment examination revealing ciprofloxacin crystals will facilitate diagnosis of crystalline nephropathy, potentially obviating need for kidney biopsy. In some cases, biopsy may be necessary to distinguish ciprofloxacin-related AIN from crystalline nephropathy as management is quite different for each. To prevent crystalline nephropathy, patients should be volume replete, ciprofloxacin should be appropriately dosed for glomerular filtration rate, and alkalinization of the urine should be avoided.[47]

Amoxicillin

Amoxicillin is a widely used antimicrobial agent. Although generally safe, it has been associated with AKI from AIN, stones, and crystalline nephropathy.[48–53] After glomerular filtration and organic anion transporter-driven tubular secretion of amoxicillin, intrarenal crystal deposition likely occurs owing to concentration-dependent oversaturation of amoxicillin and urinary crystallization in an acidic urine pH.[48–53]

After amoxicillin administration, patients present with AKI and gross hematuria and crystals in the urine. The crystals are needle or rod in shapes that can form bunches or sheaves. Risk factors for crystalline nephropathy include high amoxicillin doses, acid urine pH, and volume depletion with low urine flow rates.[48–53] Nevertheless, similar to sulfadiazine and sulfamethoxazole, no histologic evidence of intrarenal deposits of amoxicillin crystals has been published despite the association of amoxicillin with AKI and concurrent crystalluria.[48–53] Thus, kidney biopsy confirmation is lacking.

Prevention and treatment of suspected crystalline nephropathy hinge on medication discontinuation and volume repletion.[48–53] In patients with AKI, it may be useful to undertake kidney biopsy to differentiate AIN from crystalline nephropathy. With AIN, corticosteroids might be beneficial and amoxicillin would be otherwise contraindicated for future use. In patients with urine pH < 6.0, urine alkalinization may also be beneficial to prevent urinary crystal precipitation within the tubules.[48–53]

Dysproteinemia-Related Crystalline Nephropathies

Various hematologic malignancies secrete monoclonal immunoglobulins and light chains (LCs), which are an important cause of kidney disease.[4,18,54–58] Clonal plasma cells or B-cell disorders that produce these paraproteins are collectively known as dysproteinemias, which include multiple myeloma, lymphoproliferative disorders, and monoclonal gammopathy of renal significance. These secreted paraproteins may form crystals and cause crystal-related kidney injury that may involve various parts of the nephron including the preglomerular capillaries, glomeruli, and tubular system, ranging from the proximal tubules to the cortical collecting ducts.[4,18,58] It is important for clinicians and pathologists to recognize crystalline nephropathies that develop with dysproteinemias (Table 2) to allow correct diagnosis and proper management.

LC Crystalline Proximal Tubulopathy

LC crystalline proximal tubulopathy (LCPT) is a paraprotein-related kidney disease that has subtle clinical findings.[59–68] Accumulation of LCs that form crystalline structures in the proximal tubules characterizes this entity.[4,18,59–68] Owing to the proximal tubular-focused injury, full or incomplete Fanconi syndrome occurs in patients with a known or suspected dysproteinemia.[59–68] Myeloma, smoldering myeloma, monoclonal gammopathy of renal significance, and lymphoproliferative cancers are associated with LCPT.[4,18,59–68] The crystals in LCPT consist primarily of monoclonal kappa-LCs that are derived from the Vκ1 variability subgroup.[4,18,64,69]

The major kidney finding with LCPT is a proximal tubulopathy with the metabolic features of Fanconi syndrome or an isolated proximal tubular disorder (phosphate wasting, normoglycemic glycosuria, etc.). Patients may rarely have concomitant acute or chronic kidney disease.[59–63] Crystalline structures in the proximal tubules, mild acute tubular injury/atrophy, and variable degrees of interstitial fibrosis often accompany proximal tubular pathology.[4,18,59–63] Intracytoplasmic needle-shaped/geometric crystals that stain eosinophilic on H&E and JS, red on trichrome, and pale on PAS are observed within swollen proximal tubular cells.[4,18,61–63] Despite high crystal burdens, result of standard immunofluorescence staining for LC is often negative owing to the fact that antibody binding sites are shielded by the crystalline structure and are unavailable for binding.[4,18,61–63] In this setting, LC identification can be enhanced by performing immunofluorescence on formalin-fixed, paraffin-embedded sections after performing antigen retrieval with a protease such as pronase, which helps to expose some of the sequestered antibody binding sites in the crystals.[4,18,64] In addition, electron microscopy offers diagnostic

Table 2. Crystalline nephropathies associated with dysproteinemias

Dysproteinemia	Urinary crystal morphology	Renal syndromes	Histologic findings	Therapy
LC crystalline proximal tubulopathy	Crystals with needle shape and varying geometric shapes; negative/weakly birefringent on polarization	Proximal tubulopathy or full-blown Fanconi syndrome, monoclonal proteinuria, AKI, and CKD	Needle-shaped and various shaped crystals within PT cells that stain eosinophilic with H&E and JS, red with trichrome, and pale with PAS; negatively birefringent on polarization; kappa- or lambda-LC restricted on IF which may require protease/pronase digestion to allow antibody binding on IF; intracytoplasmic geometric and/or needle-shaped crystals within PT cells with some incorporated into lysosomes forming phagolysosomes on EM	Clone-directed therapy but plasma exchange is not recommended; correct metabolic disturbances (hypokalemia, metabolic acidosis, etc.) of Fanconi syndrome/proximal tubulopathy; IVFs if volume depleted; avoid nephrotoxins; supportive care
LC crystalline cast nephropathy	Crystals of varying shapes and sizes (geometric, rods, rhomboids); negative/weakly birefringent on polarization	High-grade monoclonal proteinuria, AKI, CKD, and ESKD	Geometric crystals within tubular lumens that stain eosinophilic with H&E, red with trichrome, and negative with JS; giant-cell reaction and tubulointerstitial inflammation occurs; negatively birefringent on polarization; kappa- or lambda-LC restricted on IF; crystals with geometric shapes and sharp edges on EM	Clone-directed therapy but plasma exchange and high-cutoff HD are not recommended; administer IVFs if volume depleted; avoid nephrotoxins; supportive care
Crystalglobulinemia	Crystal morphology not described	Albuminuria, hematuria, AKI, and CKD	Fractured crystals with geometric and needle shapes within vessels and glomeruli with rare intratubular crystals that stain eosinophilic with H&E, red with trichrome, pink with JS, and pale with PAS; proliferative glomeruli may occur; IgG kappa- or lambda-LC restricted on IF; dense crystals with parallel linear array substructure on EM	Clone-directed therapy, plasma exchange is recommended; IVFs if volume depleted; avoid nephrotoxins, supportive care
Crystal-storing histiocytosis	Crystal morphology not described	Fanconi syndrome, proteinuria, and AKI	Crystals with needle shapes within histiocytes and rarely within tubules that stain eosinophilic with H&E and JS, red with trichrome, and pale with PAS; chronic tubulointerstitial nephritis is present with numerous histiocytes; negative birefringence on polarization; kappa-LC restricted on IF; dense crystals with parallel linear array substructure on EM	Clone-directed therapy but plasma exchange is not recommended; avoid nephrotoxins; supportive care

AKI, acute kidney injury; CKD, chronic kidney disease; EM, electron microscopy; ESKD, end-stage kidney disease; H&E, hematoxylin and eosin; HD, hemodialysis; IF, immunofluorescence; IVF, i.v. fluid; JS, Jones methenamine silver; LC, light chain; PAS, periodic acid–Schiff; PT, proximal tubular.

benefits, especially with negative immunofluorescence staining, by revealing intracytoplasmic dense geometric and/or needle-shaped crystals within the proximal tubular cells (Figure 3a).[4,18,61–63] Crystals may be found forming within the phagolysosomes.[4,18,61–63]

Dysproteinemia-related LCPT requires clone-directed therapy. Plasma exchange offers no benefit and is not recommended to reduce LC concentrations. Prognosis for remission from proximal tubulopathy and overall kidney recovery seems variable depending on severity of tubulointerstitial disease[59–63]

LC Crystalline Cast Nephropathy

Classical LC cast nephropathy is one of the most common kidney lesions described in patients with multiple myeloma.[4,18,58,65–68] Patients with LC cast nephropathy come to clinical attention when AKI and proteinuria, and sometimes CKD, develop in the setting of paraproteinemia.[58,65–68] Nevertheless, dysproteinemia may only be recognized after kidney biopsy. After the workup, ∼80% to 90% of patients meet the myeloma criteria.[65] Other findings suggestive of myeloma, such

as hypercalcemia, bone pain, or anemia, may also be present.[65–69]

A potential dysproteinemia should be considered when the urinalysis result reveals a disparity in dipstick albumin (negative/trace) with urine nonalbumin (Bence Jones) proteinuria.[58,65–69] Negatively or weakly birefringent crystals of varying geometric shapes, sometimes forming a cast (Figure 3b), can sometimes be found in the urine sediment.[4,14,65–69] Importantly, histologic findings in LC crystalline cast nephropathy are quite different than those of the classic "PAS negative fractured cast" typically noted with classical LC cast nephropathy.[4,18,65–69] Rather, geometric crystals that stain eosinophilic on H&E and red on trichrome are observed (Figure 3c).[4,18] Result of PAS staining is variable and that of JS stain is generally negative, and the crystals are birefringent on polarization.[4,18] A monocytic/giant-cell reaction and tubulointerstitial inflammation often accompany the crystals. Kappa- or lambda-LC restriction on immunofluorescence staining documents monoclonality. Furthermore, result of electron microscopy reveals dense crystals that have geometric shapes and sharp edges.[4,18,65–69]
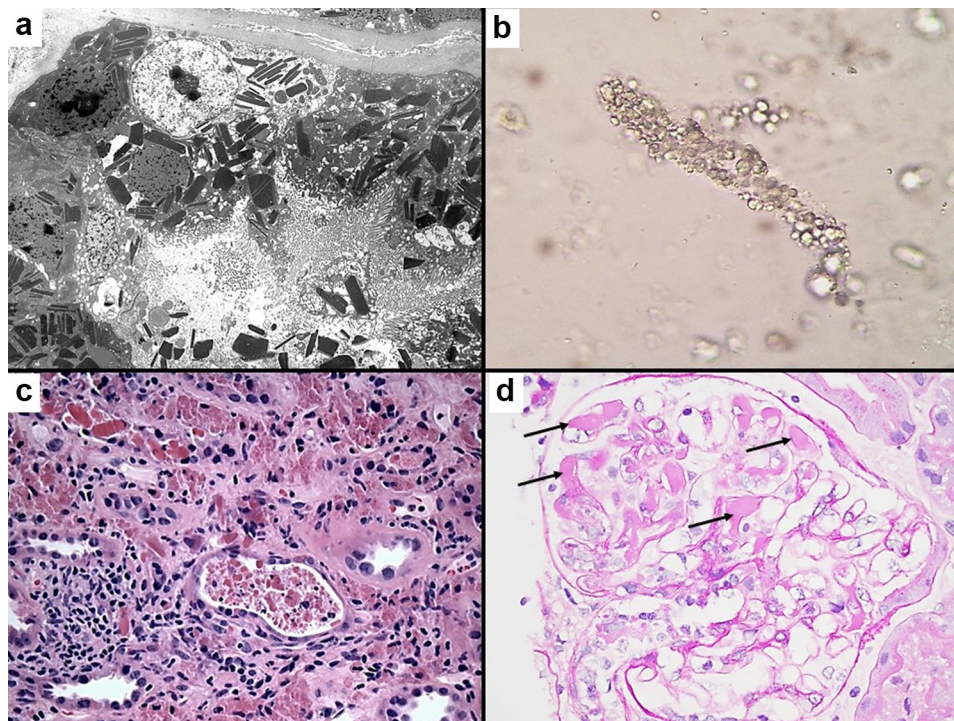
Figure 3. Various crystals found in the urine sediment results and kidney biopsy findings in patients with dysproteinemia-related crystalline nephropathies. (a) Light chain crystals with geometric shapes are noted within the proximal tubular cells on electron microscopy in a patient with light chain proximal tubulopathy. (b) Light chain crystals of varying sizes and shapes are observed within a urinary cast. (c) Light chain crystals exhibit red staining with H&E by routine light microscopy in a patient with light chain crystalline cast nephropathy. (d) Light chain crystals within the glomerular capillaries are observed on routine light microscopy in a patient with crystalglobulinemia (periodic acid–Schiff staining, ×400). H&E, hematoxylin and eosin.

When LC crystalline cast nephropathy is diagnosed, clone-directed therapy is the most important treatment. Although dialysis may be required as supportive care, the utility of plasma exchange and high-cutoff hemodialysis is unclear and not currently recommended to remove LCs. Prognosis for kidney recovery seems variable and not universal but has recently been improved with the availability of new drugs.[4,65–69] Severity of tubulointerstitial disease likely plays an important role in determining recovery.

Crystalglobulin-Induced Nephropathy

Patients with dysproteinemia may also develop the rare but interesting disorder known as crystalglobulinemia.[70–73] The formation of microcrystals within the systemic blood vessels and vasculature of the kidneys in these crystalline disorders leads to vascular injury with thrombosis/occlusion and end-organ damage.[18,70–73] In addition, the crystals from these disorders may be found within the tubular lumens.

Increased serum creatinine and albuminuria along with various systemic manifestations, such as arthralgias and rash, characterize the clinical presentation.[70–74] Urinalysis results reveal hematuria and proteinuria, whereas kidney histologic findings reveal crystal deposition within the vasculature and glomerulus, although intratubular crystals have also been described.[70–73] The crystals have geometric shapes that fracture and stain eosinophilic on H&E (Figure 3d), red on trichrome, pink on JS, and pale on PAS.[18,70–73] Proliferative glomeruli may be present when leukocytes and monocytes engulf the crystals.[18,70–73] IgG kappa- or lambda-restricted staining is noted on immunofluorescence, whereas crystals are dense with parallel linear array substructure on electron microscopy.[18,70–73]

As with all dysproteinemias, management hinges on treating the clonal disorder to reduce paraprotein production, and using plasma exchange to rapidly remove circulating paraproteins is recommended for this disorder.[70–73] Unfortunately, limited data note a relatively poor prognosis with high fatality rate.

Crystal-Storing Histiocytosis Nephropathy

Another rare paraprotein-related crystalline nephropathy is crystal-storing histiocytosis, which is a systemic disease that has overlap with LCPT.[4,18,74–77] LC crystal accumulation within the histiocytes in various extrarenal organs characterizes this entity; rare kidney involvement also occurs.[74–77] Crystal-storing histiocytes are found predominantly in the tubulointerstitium and less frequently in the glomerular mesangium and capillary loops.[4,18,74,75] LCs from the

Table 3. Crystalline nephropathies associated with inherited disorders

Inherited disorder (inheritance and defect)	Urinary crystal morphology	Kidney syndromes	Histologic findings	Therapy
Cystinosis (autosomal recessive; lysosomal storage disease)	Translucent needles, rods, or geometric shapes; Positively birefringent on polarization	Fanconi syndrome, AKI, CKD, and ESKD	Needle- or geometric-shaped crystal footprints in podocytes, mesangial cells, and interstitial macrophages; less common in tubular cells and tubules; positively birefringent on polarization	Oral cysteamine; treat metabolic abnormalities (hypokalemia, metabolic acidosis, etc.) of Fanconi syndrome; supportive care including dialysis and kidney transplantation
2,8-Dihydroxyadeninuria or APRT deficiency (autosomal recessive; deficiency of adenine phosphoribosyltransferase)	Round with central spicules, reddish-brown color and dark outline; positively birefringent on polarization	Crystalluria, cylinduria, nephrolithiasis, AKI, CKD, and ESKD	Crystals that are brown to green color on H&E and PAS, light blue on trichrome, black on JS; irregular or fan-shaped crystals within tubules; positively birefringent on polarization	Xanthine oxidase inhibition (allopurinol or febuxostat) therapy early in the course; supportive care including dialysis and kidney transplantation
Primary hyperoxalurias 1, 2, and 3 (autosomal recessive; hepatic deficiency of glyoxylate metabolism)	Calcium oxalate -Dihydrated: translucent bipyramidal shapes; positively birefringent (weak) on polarization -Monohydrated: translucent ovoids, dumbbells, and rods; positively birefringent on polarization	Crystalluria, cylinduria, nephrolithiasis, AKI, CKD, and ESKD	Crystals that are translucent to pale blue crystals with fan-like or sunburst shapes within tubular lumens, tubular cells, and interstitium; interstitial inflammation near crystals also noted; positively birefringent on polarization	Administer IVFs if hypovolemic; oral citrate and pyridoxine; supportive care with dialysis, kidney ± liver transplantation; lumasiran approved by FDA and EU; stiripentol being studied in clinical trials
Dent disease type 1 (X-linked recessive; mutation in CLCN5 gene) Dent disease type 2 (X-linked recessive; mutation in OCRL1 gene)	Calcium oxalate, calcium phosphate, mixed -See calcium oxalate crystals Calcium phosphate -Amorphous or thick rods	Type 1: crystalluria, proximal tubulopathy/ Fanconi syndrome, hypercalciuria, nephrocalcinosis, nephrolithiasis, CKD, and ESKD Type 2: same as type 1	Rare calcium phosphate crystals in corticomedullary junction; focal global glomerulosclerosis; nonspecific findings with tubular atrophy, interstitial inflammation, and fibrosis	Reduction in hypercalciuria with thiazide diuretics; oral citrate: oral potassium, phosphate, and vitamin D; supportive care with dialysis/transplantation for ESKD
Lowe syndrome (X-linked recessive; mutation in OCRL1 gene)	Calcium oxalate, calcium phosphate, mixed -See calcium oxalate crystals Calcium phosphate -Amorphous or thick rods	Crystalluria, proximal tubulopathy/Fanconi syndrome, distal RTA, hypercalciuria, nephrocalcinosis, nephrolithiasis, CKD, and ESKD	Rare calcium-phosphate crystals are found; focal glomerulosclerosis; nonspecific findings with tubular atrophy, interstitial inflammation, and fibrosis	Oral bicarbonate, potassium, phosphate and vitamin D; supportive care with dialysis/ transplantation for ESKD

AKI, acute kidney injury; APRT, adenine phosphoribosyltransferase; CKD, chronic kidney disease; ESKD, end-stage kidney disease, EU, European Union; FDA, US Food and Drug Administration; H&E, hematoxylin and eosin; IVF, i.v. fluid; JS, Jones methenamine silver; PAS, periodic acid–Schiff; RTA, renal tubular acidosis.

Vκ1 variability subgroup with several unusual amino acid substitutions seem to promote crystallogenesis, prevent intralysosomal degradation, and underlie the disease process.[4,18]

Clinical manifestations include AKI, proteinuria, and Fanconi syndrome.[74–77] Histologically, chronic tubulointerstitial nephritis with numerous histiocytes is noted.[4,18,74–77] Crystals, which are geometric and needle shaped on light and electron microscopy, are similar to those found with LCPT except that the crystals are located within the histiocytes rather than the tubular cells.[4,18,74–77] Immunofluorescence stains positive for monoclonal kappa-LCs.

As in other dysproteinemias, therapy is directed at the clonal disorder to stop paraprotein production. There is no role for plasma exchange. Crystal-storing histiocytosis is associated with a slow loss of kidney function and generally has a good prognosis.[74–77]

Crystalline Nephropathies Associated With Inherited Disorders

A number of crystalline nephropathies of clinical interest result from a number of inherited disorders. Disordered enzyme metabolism or defective molecule transport leads to crystal formation and precipitation within the kidneys. Crystalline nephropathies owing to cystinosis, 2,8-dihydroxyadenine, primary hyperoxaluria (PH), and Dent disease and Lowe syndrome are discussed (Table 3).

Crystalline Nephropathy From Cystinosis

Kidney disease occurs with cystinosis, a rare, inherited disease characterized by defects in cystine transport across the lysosomal membranes which result in systemic cystine accumulation and crystallization.[78,79] Mutations in *CTNS* gene, which codes cystinosin, are the primary cause of aberrant cystine transport.[78,79] The disease occurs most often in infants, with a more severe and potentially lethal form of cystinosis occurring and leading to failure to thrive.[78–80] A few cases occur in adolescence or adulthood and tend to have mild CTNS gene mutations.

Kidney involvement manifests in most cases in the first year of life with infantile cystinosis.[78–80] Proximal tubular dysfunction including a full Fanconi syndrome may be found. Over time, progressive CKD and end-stage kidney disease (ESKD) eventually occur. Cystine crystals accumulate predominantly in podocytes, mesangial cells, and interstitial macrophages, although they may also deposit in tubular cells and within the tubular lumens.[4,18,78] Crystals with needle-like or geometric shapes are observed within the cells with frozen specimens, but are otherwise dissolved out during routine tissue processing.[4,18] When crystals are present, they are strongly birefringent on polarization.[4,18,78]

Standard therapy for cystinosis includes oral cysteamine, which enhances cystine clearance.[81,82] Cysteamine dosing is currently guided by the leukocyte cystine levels of the patient. Plasma chitotriosidase enzyme activity, an enzyme produced by macrophages activated by cystine, was recently found to be a biomarker of both cellular cystine burden and inflammation and excellent predictor of leukocyte cystine levels.[81] It is possible that this biomarker may be a better guide for cysteamine dosing. Although this therapy slows crystal deposition, it is not a cure and patients develop progressive kidney failure.[81,82] In search of a more curative treatment, preclinical studies using HSPC gene cell therapy have been successfully used in a mouse model of cystinosis.[82] Reduced tissue cystine content and improved kidney function were noted in an *ex vivo* gene-modified HSPC strategy using self-inactivating lentivirus carrying *CTNS* cDNA (pCCL-CTNS). On the basis of these exciting data, it is hoped that pharmacologic and toxicologic studies will reveal safety and efficacy and phase I/II human clinical trials will be undertaken.[82]

Crystalline Nephropathy From 2,8-Dihydroxyadenine

The 2,8-dihydroxyadeninuria or adenine phosphoribosyltransferase deficiency is an autosomal recessive disorder that occurs owing to loss of adenine phosphoribosyltransferase function.[83,84] This defect in enzyme function shunts adenine away from adenine monophosphate formation to 8-hydroxyadenine and 2,8-hydroxyadenine formation by xanthine oxidase. These crystals are highly insoluble in the urine and precipitate in the tubular lumens. The main clinical manifestations of this inherited disorder are nephrolithiasis and crystalline nephropathy.[83,84]

Delayed recognition and treatment of 2,8-dihydroxyadeninuria may lead to progressive CKD and ESKD.[83–85] Although stone analysis is diagnostic, urine sediment examination revealing round 2,8-dihydroxyadenine crystals that are reddish-brown with central spicules (Supplementary Figure S1A) provides critical information.[14] Notably, these crystals are birefringent and have a Maltese cross appearance on polarization, and crystal-containing casts may also be found. On kidney biopsy, intratubular crystals have irregular and fan-like shapes and stain faint brownish-green color on H&E (Supplementary Figure S1B) and PAS, light blue on trichrome, and silver positive on JS.[4,18,83] As in the urine, the crystals are strongly birefringent on polarization.[4,14] When examining the kidney tissue, it is important for pathologists to

distinguish these crystals from similar appearing calcium oxalate and triamterene crystals.[4,18,83]

On recognition of this inherited disorder, timely treatment with xanthine oxidase inhibitors, such as allopurinol or febuxostat, prevents further crystal deposition.[83–85] This approach can improve or stabilize kidney function for many patients. Dialysis therapy and kidney transplantation with xanthine oxidase therapy to prevent recurrent crystalline-related kidney disease are pursued when ESKD develops.

Crystalline Nephropathy From PH

PHs are autosomal recessive disorders that result in calcium oxalate-related kidney disease owing to defects in the enzymes of glyoxylate metabolism.[86–88] Excessive production of glyoxylate by the liver leads to increased oxalate synthesis, elevated plasma oxalate levels, and hyperoxaluria. As a result, calcium oxalate crystals deposit within the renal tubular lumens, which causes urinary obstruction, direct cytotoxicity, and necroinflammation. Although symptomatic nephrolithiasis is common, calcium oxalate crystalline nephropathy occurs in up to 50% of patients. PH-1 is the most common, and kidney involvement often leads to CKD and ESKD.[86–88] Urine sediment examination may reveal monohydrated (Supplementary Figure S1C) and/or dihydrated calcium oxalate crystals that can be free and/or found within casts. Histologic evaluation of the kidneys reveals crystals within the tubules that are birefringent on polarization (Supplementary Figure S1D). Pediatric and adolescent patients with oxalate nephropathy of unclear origin should undergo testing for these genetic disorders.

Standard management includes oral potassium citrate, volume repletion, and pyridoxine supplementation along with genetic counseling. When ESKD develops, dialysis and kidney alone or along with liver transplantation (primarily for PH-1) are also undertaken.[86–88] New therapies for PH have recently become available. Lumasiran given s.c. is a small interfering RNA medication that targets hydroxyacid oxidase-1 gene and silences mRNA-encoding glycolate oxidase. Through this effect, lumasiran depletes glycolate oxidase and inhibits oxalate synthesis thereby significantly reducing hyperoxaluria.[88,89] One dose of this drug reduced urinary oxalate concentration up to 50% in a PH-1 genetic mouse model and up to 98% with multiple doses in a rat model of hyperoxaluria.[88,90] Illuminate-A, the phase 3 clinical trial in patients with PH aged ≥6 years and estimated glomerular filtration rate ≥30 ml/min per 1.73 m^2, revealed a 65% reduction in 24-hour urinary oxalate at 6 months with no adverse effects.[91] Lumasiran also achieved statistically significant results for all 6 secondary end points

in the trial. Lumasiran has been approved by the US Food and Drug Administration and European Union for PH-1 therapy in pediatric and adult patients.[89]

The oral antiepileptic drug stiripentol, a neuronal lactate dehydrogenase-5 isoenzyme inhibitor, represents another potential treatment for calcium oxalate crystalline nephropathy.[88,92–94] On the basis on *in vitro* and *in vivo* animal studies targeting hepatic lactate dehydrogenase metabolism, both gene therapy and stiripentol reduced hepatocyte oxalate synthesis and urine oxalate excretion.[88,92–94] Using ethylene glycol intoxication and oxalate nephropathy models, stiripentol significantly reduced urine oxalate excretion.[94] Although stiripentol failed to reduce plasma oxalate concentrations in patients with dialysis-dependent PH-1,[95] further study in clinical trials for oxalate-related kidney disease is warranted.

Nephrocalcinosis From Dent Disease and Lowe Syndrome

Two rare inherited disorders associated with nephrocalcinosis include Dent disease and Lowe syndrome (Table 3). Dent disease types 1 and 2 are both X-linked recessive disorders that are due to mutations in the CLCN5 and OCRL1 genes, respectively.[83,96–98] Both types of Dent disease manifest a proximal tubulopathy or full Fanconi syndrome and hypercalciuria, which is generally complicated by nephrocalcinosis and nephrolithiasis.[83,96–98] Interestingly, hypercalciuria is due to both excessive calcium absorption in the gastrointestinal tract and defective proximal tubule calcium uptake.[99] Calcium oxalate and calcium phosphate crystals may be visualized in the urine sediment along with erythrocytes, especially with kidney stones. Patients can progress to CKD and ESKD over time. Other potential findings include osteomalacia from renal phosphate wasting.[83,96–98] Patients with type 2 Dent disease may also develop cataracts, intellectual disability, and hypotonia.[96–98,100] Treatment is primarily supportive including thiazide diuretics to reduce hypercalciuria, oral citrate to reduce nephrolithiasis, oral potassium, phosphate and vitamin D repletion, and dialysis and transplantation when ESKD develops.[83,96–98]

Lowe (oculocerebrorenal) syndrome (Table 3) is very similar to Dent disease type 2 and is also an X-linked recessive disorder that is due to a mutation in the OCRL1 gene.[83,100–103] The kidney manifestations are similar including proximal tubulopathy, nephrocalcinosis, and nephrolithiasis but can also include distal renal tubular acidosis.[83,100–103] Similar to Dent disease type 2, patient can have cataracts, hypotonia, and intellectual disability. The urine sediment findings are similar to Dent disease, whereas progression of CKD is typically more rapid in Lowe syndrome versus Dent

disease.[83,100–103] Therapy is supportive with repletion of oral bicarbonate/citrate, potassium, phosphate, and vitamin D, whereas dialysis and transplantation are options when ESKD develops.[83,100–103]

Conclusion

The crystalline nephropathies are a unique form of kidney disease. Direct and indirect crystal-related injuries including pathways on inflammation and necroinflammation underlie kidney injury. Clinicians and pathologists should be aware of the causes of crystalline nephropathy, including medications, dysproteinemias, and inherited disorders. Diagnosis hinges on urine sediment examination results and kidney biopsy findings revealing intrarenal crystals.

DISCLOSURE

MAP is the deputy editor for *Kidney360*, co–editor-in-chief for the *Journal of Onco-Nephrology*, AKI section editor for *Clinical Nephrology*, on the editorial board for a number of kidney and medicine journals, and an author for UpToDate. LCH is on the editorial board of *Kidney360* and is a consultant to ChemoCentryx.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Various crystals found in the urine sediment results and kidney biopsy findings in patients with inherited crystalline nephropathies.

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