

# Adenine Phosphoribosyltransferase Deficiency: A Potentially Reversible Cause of CKD



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Adenine phosphoribosyltransferase (APRT) enzyme deficiency is an important and potentially reversible cause of progressive chronic kidney disease. It is a rare, autosomal recessive disorder that was first described in 1974<sup>1</sup> with more than 40 known mutations<sup>2,3</sup> and estimated prevalence of 1 in 50,000 to 100,000 persons.<sup>2,4,5</sup> The APRT enzyme is important for the conversion of adenine to adenosine monophosphate in the salvage purine pathway. Deficiency of this enzyme results in the metabolism of adenine into 2,8-dihydroxyadenine (DHA) by xanthine oxidase (xanthine dehydrogenase) (Figure 1a). DHA is highly insoluble in urine and will precipitate to cause either urolithiasis or crystal nephropathy. There are no known extrarenal manifestations and reasons for this remains unclear given the extensive tissue distribution of this enzyme.

The typical appearances of DHA crystals on renal biopsy are of yellow-brown needle-shaped crystals, which are arranged in spherical, radial, or irregular aggregates and are birefringent under polarized light. Tubular injury, deposition, and obstruction can occur, and foreign body reaction with histiocytes can be seen surrounding some of the crystals. Left untreated, chronic crystal deposition in the kidney can lead to irreversible tubular atrophy and interstitial fibrosis. Crystalluria is characterized by birefringent yellow-brown crystals that are round in appearance and display a Maltese cross pattern on polarized light microscopy.

Although it can present in any age group and stage of disease, it is most commonly diagnosed in adults

(median age 36 years<sup>2</sup>), with up to 15% of patients diagnosed either in end-stage renal failure or following kidney transplantation.<sup>3,4</sup> APRT deficiency also may be misdiagnosed, as other forms of renal stone disease, crystal nephropathy, or chronic kidney disease of unknown etiology.<sup>2</sup> The diagnosis of APRT deficiency in patients with urolithiasis or crystal nephropathy is based on the following: (i) genetic mutation testing; (ii) absent or reduced APRT enzyme activity in red cell lysates; or (iii) confirmation of DHA crystal composition by infrared spectroscopy (Figure 1b).

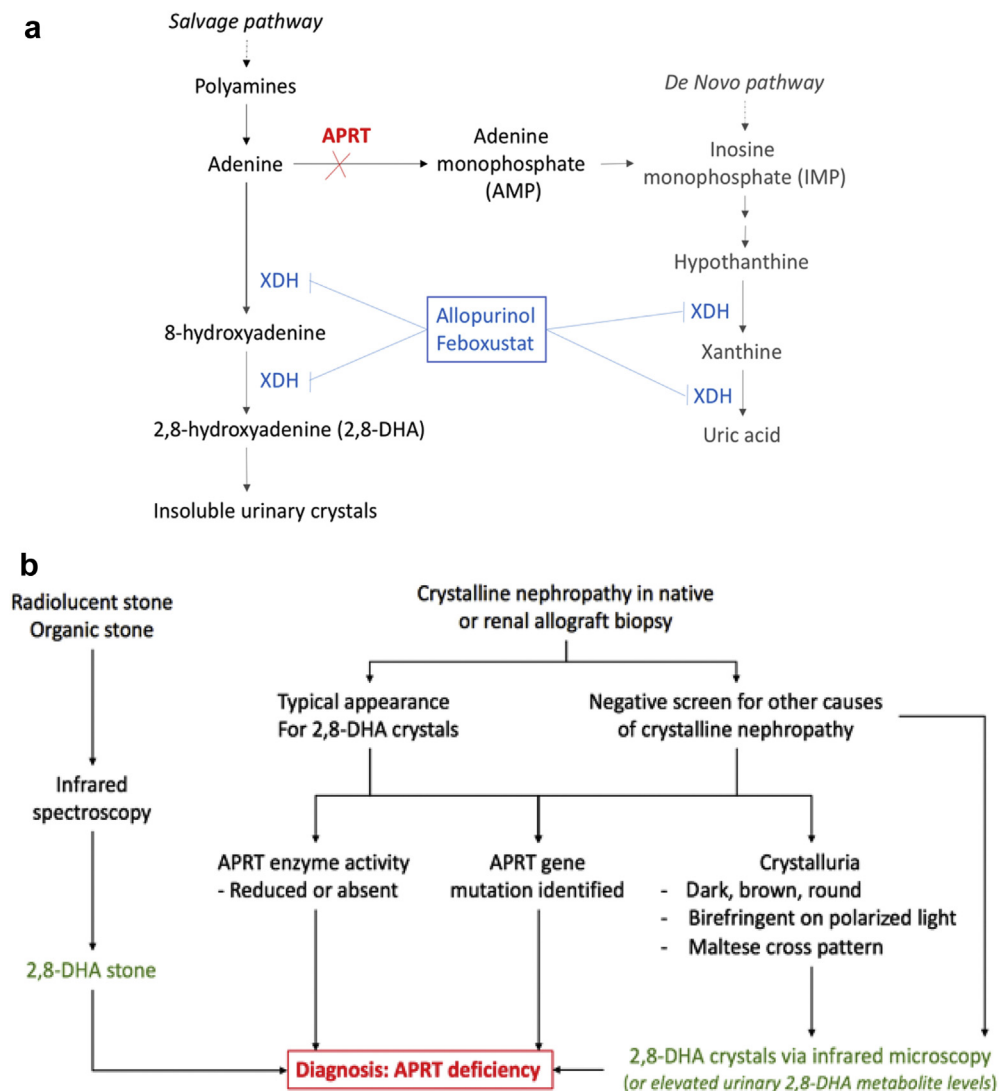
Reducing DHA production by xanthine oxidase inhibition is the cornerstone of pharmacological therapy for APRT deficiency. Allopurinol is the most used drug in this instance, whereas the addition or switch to febuxostat has been used in several cases.<sup>2,6</sup> Supportive therapy includes low purine diet and high fluid intake. Urinary alkalinization is ineffective, as DHA remains insoluble at physiological urine pH ranges.<sup>5</sup>

We present 3 cases (Tables 1 and 2) that highlight the diagnostic pitfalls and challenges in management, particularly in the transplantation setting. For further details to this article, please refer to the [Supplementary Methods](#) and [Supplementary References](#).

## RESULTS

### Case 1

A 47-year-old Caucasian gentleman presented in 2013 for evaluation of renal impairment on a background of



**Figure 1.** (a) Purine metabolism pathway. In the absence of adenine phosphoribosyltransferase (APRT) enzyme activity, adenine is converted into 8-hydroxyadenine and 2,8-dihydroxyadenine (DHA) by xanthine oxidase (XDH, also known as xanthine dehydrogenase). DHA becomes insoluble and precipitates in the urine to cause crystal nephropathy and/or urolithiasis. (b) Suggested diagnostic pathway for APRT deficiency. Patients presenting with urolithiasis and found to have “organic” stone on analysis ideally should have the stone analyzed by infrared mass spectroscopy to confirm DHA composition. Patients presenting with crystalline nephropathy of uncertain cause, or with the typical appearance for DHA crystals, should have confirmation testing by (i) demonstration of reduced or absent APRT enzyme activity on red cell lysates, (ii) identification of homozygous gene mutation, or (iii) crystalluria sent for infrared mass spectroscopy to confirm composition.

obesity, hypertension and atrial fibrillation. At the time of presentation, the serum creatinine (SCr) was 356  $\mu\text{mol/l}$  (estimated glomerular filtration rate 17 ml/min per 1.73  $\text{m}^2$ ) and subnephrotic proteinuria of 0.92 g/d without microscopic hematuria. This is compared with baseline SCr 119  $\mu\text{mol/l}$  measured 5 years previously. The hemoglobin A1c, autoimmune, and myeloma serology were all unremarkable. Computed tomography scan showed 8.5 cm kidneys without evidence of calculi or hydronephrosis. A native renal biopsy revealed global sclerosis in 15 of 18 glomeruli and multiple, yellow-brown tinged crystals in the tubular lumen, epithelial cytoplasm, interstitium, with associated giant cells, marked tubular atrophy, and diffuse interstitial fibrosis. The crystals ranged from needle to rod to rhomboid in

shape and were birefringent under polarized light. Congo red was negative and immunofluorescence was nondiagnostic. Electron microscopy revealed unremarkable glomerular features, no evidence of electron-dense deposits, but noted needle-shaped crystals in some tubules. A 24-hour urine collection was unremarkable except for hypocitraturia (0.4 mmol/d).

Given the unusual crystal appearance, APRT deficiency was suspected and subsequent testing confirmed this diagnosis with reduced APRT enzyme activity (0.1 nmol/min per mg; normal  $>0.15$  nmol/min per mg) and elevated urinary 2,8-dihydroxyadenine (28 mmol/mol; normal  $<13$  mmol/mol). Despite treatment with allopurinol (100 mg/d), he progressed to be dialysis dependent 2 months after presentation.

**Table 1.** Baseline characteristics of the 3 patients, before transplantation in cases 1 and 2

Patient characteristics	Case 1	Case 2	Case 3
Age, yr, at diagnosis	47	52	23
Gender	Male	Female	Male
Race	Caucasian	Lebanese	Lebanese
Comorbidities	Obesity, hypertension, atrial fibrillation	Graves disease	Obesity, atrial flutter
Urolithiasis	No	No	Yes
Family history of kidney disease	No	No	No
Creatinine at presentation, $\mu\text{mol/l}$	356	268	1020
Proteinuria, g/24 h	0.92	1.09	0.23
Microscopic hematuria	No	No	No
Native kidney biopsy	LM: 15/18 globally sclerosed glomeruli; tubular, epithelial and interstitial birefringent, brown crystal deposition with diffuse interstitial inflammation and fibrosis. IF: nondiagnostic EM: Needle-shaped crystals in some tubules	LM: 6 of 10 globally sclerosed glomeruli; golden brown, birefringent tubular crystals with associated diffuse interstitial fibrosis and inflammation. IF: nondiagnostic EM: nondiagnostic	LM: 5 of 17 globally sclerosed glomeruli; yellow-brown, birefringent tubular crystals with associated diffuse interstitial fibrosis. IF: nondiagnostic EM: nondiagnostic
Provisional diagnosis	APRT deficiency	Chronic interstitial nephritis	Oxalate nephropathy
Time from presentation to dialysis (modality)	2 mo (hemodialysis)	3 yr (peritoneal dialysis)	<1 wk (hemodialysis)
Time from native biopsy to APRT diagnosis	10 wk	6 yr	10 mo
Genetic testing	Not done	Homozygous c.188G>A (p.Gly63Asp)	Homozygous c.188G>A (p.Gly63Asp)
APRT enzyme activity, nmol/min per mg	0.1	0.11	0.09
Urine stone analysis	NA	NA	Organic material
Urine 2,8-DHA	28 mmol/mol	Not available	Not available
Urine biochemistry	Hypocitraturia	Hypocitraturia	Hyperoxaluria
Urine microscopy	Yes, but assessed only posttransplant		Birefringent crystals

APRT, adenine phosphoribosyltransferase; EM, electron microscopy; IF, immunofluorescence; LM, light microscopy; mo, month; NA, not applicable; wk, week; y, yr. Normal APRT enzyme activity > 0.15 nmol/min per mg and spot urine 2,8-DHA <13 mmol/mol.

His allopurinol was increased to 150 mg daily when he received a deceased renal transplant in January 2018. He had delayed graft function and the implant

biopsy showed acute tubular injury, and a repeat biopsy at day 10 demonstrated recurrence of crystal nephropathy with borderline rejection with interstitial

**Table 2.** Post-kidney transplant course for patients 1 and 2

	Case 1	Case 2
Transplantation	January 2018	May 2017
APRT diagnosis before transplantation	Yes	No
Allopurinol dose pretransplant	150 mg (for 4.5 yr)	No
Delayed graft function	Yes	Yes
Implantation biopsy	Acute tubular injury	Acute tubular injury
Time from transplant to crystal detection, d	10	24
Maximal allopurinol dose, mg	600	300
Oxypurinol trough, mg/l	21–32	30–36
Drug reaction with eosinophilia and systemic symptoms or ocular involvement	Nil	Nil
Febuxostat	40 mg	Nil
Crystalluria posttransplant	Detected 4 mo post	Not detected 12 mo post
Treatment for rejection	Yes, pulse methylprednisolone	Yes, methylprednisolone and 6 mg/kg antithymocyte globulin (day 24 for Banff grade 2A rejection: i1, t1, v1, ptc2, c4d-ve)
Other complications	Invasive CMV disease (graft CMV nephritis; colitis)	BK virus-associated nephropathy Shingles (reactivation of varicella zoster) CMV viremia Urinary tract infections
Three-mo posttransplant biopsy	Involved 15% of biopsy (less) No rejection: ci2, ct2, cv1, ah1	No rejection: 15% crystals ci3, ct3, cv1, ah0
Three-mo posttransplant GFR/DTPA, ml/min per 1.73 m <sup>2</sup>	52	42
Twelve-mo posttransplant biopsy	Not available	No rejection: 15% crystals ci3, ct3, cv1, ah0
Last available creatinine level, $\mu\text{mol/l}$	164 (6 mo post)	145 (12 mo post)
Maintenance immunosuppression	Tacrolimus, mycophenolate, prednisolone	Tacrolimus, mycophenolate, prednisolone

APRT, adenine phosphoribosyltransferase; CMV, cytomegalovirus; DTPA, technetium-99m diethylene-triamine-pentaacetic acid; GFR, glomerular filtration rate; mo, month; yr, year.



inflammation and tubulitis. He received intravenous methylprednisolone (total of 1500 mg), and allopurinol was increased to 400 mg daily. Subsequent biopsy on day 21 showed similar findings (crystal nephropathy, borderline rejection) and he received further pulse methylprednisolone. His renal function improved, no longer needing dialysis at 3 weeks posttransplant, and reached a trough SCr 180  $\mu\text{mol/l}$ . His allopurinol was up-titrated to a maximum tolerated dose of 600 mg daily (limited by diarrhea) and trough oxypurinol levels varied between 21 and 32 mg/l. Surveillance urine microscopy (Figure 2e and f) showed persistent crystalluria and 20 mg of feboxustat was introduced, in addition to allopurinol 600 mg daily.

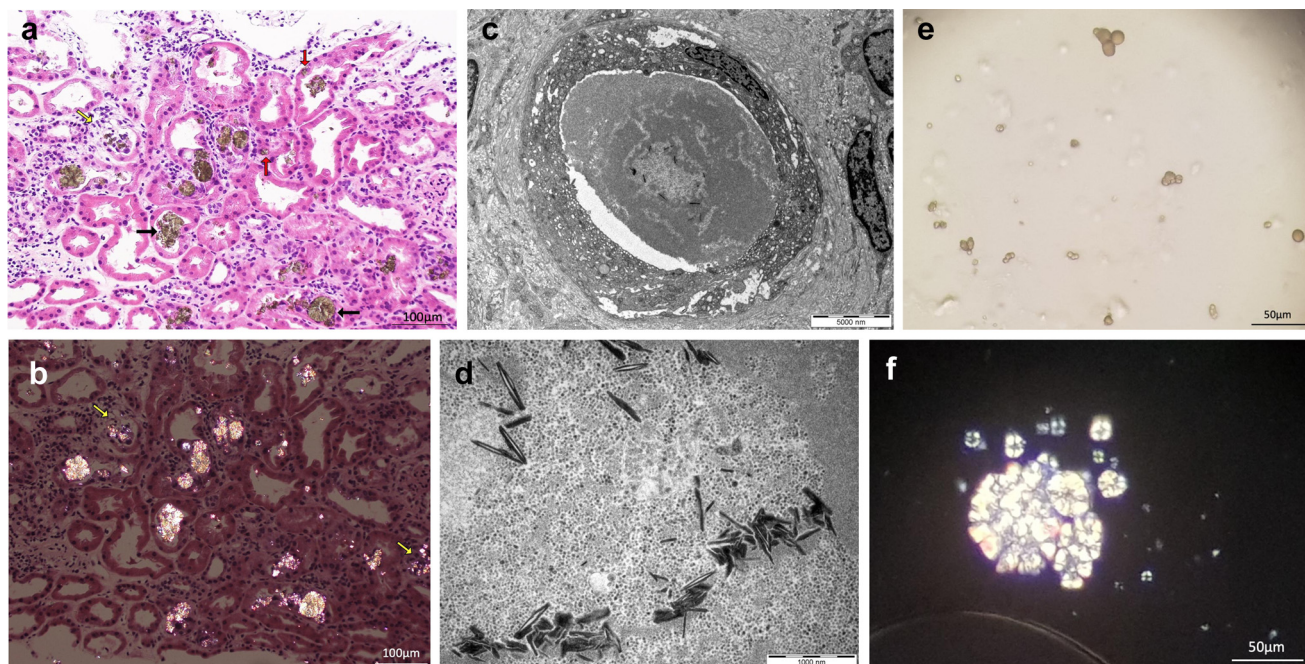
Four-months after transplantation, he developed invasive cytomegalovirus (CMV) disease and a repeat biopsy (Figure 2a–d) with SCr 270  $\mu\text{mol/l}$  showed acute tubular injury, crystalline nephropathy, and CMV inclusions. His renal function improved to SCr 164  $\mu\text{mol/l}$  following treatment of CMV disease and up-titration of feboxustat to 60 mg daily. He developed a facial rash, which was diagnosed as rosacea and resolved with a short course of doxycycline.

Baseline characteristics of all 3 cases and the post-transplant course are summarized in Tables 1 and 2.

### Case 2

A 52-year-old Lebanese woman was investigated for progressive kidney disease with SCr 97  $\mu\text{mol/l}$  rising to 268  $\mu\text{mol/l}$  (estimated glomerular filtration rate 54 and 17 ml/min per 1.73  $\text{m}^2$ , respectively) over 4 months. She had subnephrotic proteinuria (1.09 g/24 hours) without microscopic hematuria, and the renal ultrasound showed atrophic left kidney and 12.5 cm right kidney. The renal biopsy showed diffuse interstitial inflammation and fibrosis with the occasional golden brown, birefringent intratubular crystals, and this was attributed to ciprofloxacin-associated chronic interstitial disease, and she progressed onto peritoneal dialysis 3 years later.

She received a deceased renal transplant and required 2 sessions of hemodialysis for delayed graft function. A biopsy day 3 posttransplant showed acute tubular injury and borderline rejection, which was treated with methylprednisolone. Her renal function improved to SCr 220  $\mu\text{mol/l}$  but then deteriorated to



**Figure 2.** (a) Light microscopy renal biopsy images of adenine phosphoribosyltransferase (APRT) deficiency. Hematoxylin and eosin stain (H&E; original magnification  $\times 20$ ) of the 3-month protocol transplant biopsy of case 1 showing ongoing crystal deposits, predominantly in the tubular lumen (black arrows) and associated with foreign body reaction and acute tubular injury. Crystals also are seen within the epithelial layer in some of the injured or atrophic tubules (red arrows). One tubule demonstrated the disruption of the tubular basement membrane and the release of crystalline material into the interstitium (yellow arrow). (b) Polarized image of the renal biopsy (of Figure 1a) demonstrating birefringent crystals and highlighting the locations of the crystals, which are more subtle on the H&E sections. The areas of tubular rupture and the release of crystals into the interstitium are highlighted (yellow arrows). Bar = 100  $\mu\text{m}$ . (c) Electron microscopy of APRT deficiency demonstrating luminal obstruction with the crystalline aggregates. Bar = 5000 nm. (d) Higher-power view of the electron microscopy image within the luminal aggregate (in Figure 2c) revealing needle-like substructures. Bar = 1000 nm. (e) Crystalluria in APRT deficiency. Typical appearance of spherical, brown crystals seen on urine microscopy at original magnification of  $\times 20$ . (f) Crystalluria in APRT deficiency under polarized light demonstrating birefringent crystals with a maltese cross pattern at original magnification of  $\times 40$ .

SCr 262  $\mu\text{mol/l}$  after a period of subtherapeutic tacrolimus levels. A biopsy at day 24 showed Banff grade 2A T-cell-mediated rejection (Banff scores: i1, t1, v1, ptc2), positive simian virus (SV40) stain, and tubular and interstitial crystal deposition.<sup>7</sup> She received antithymocyte globulin (total 6 mg/kg) with improvement from peak SCr 327  $\mu\text{mol/l}$  to SCr 243  $\mu\text{mol/l}$ .

Oxalate nephropathy was suspected, but 24-hour urine metabolic screen was unremarkable except for hypocitraturia (<2 mmol/d). With the experience in case 1, we tested for and confirmed APRT deficiency with reduced APRT enzyme activity (0.11 nmol/min per mg). Genetic testing confirmed homozygous *c.188G>A*; *p.Gly63Asp* mutation (an identified pathogenic APRT gene mutation). Urine DHA testing was now unavailable. The patient was commenced on allopurinol at 5 weeks posttransplant, tolerating 300 mg/d (corresponding trough oxypurinol levels 35–36 mg/l), again, limited by diarrheal symptoms.

Despite the positive SV40 stain, both blood and urine polymerase chain reaction testing for polyoma and BK virus were negative and hence not initially treated. A repeat biopsy 2 weeks later showed persistent crystals and positive SV40 in 2 nuclei and despite repeatedly negative blood and urine polyoma virus on polymerase chain reaction, so she was treated with intravenous immunoglobulin (IV.Ig) with improvement of SCr to 130 to 150  $\mu\text{mol/l}$ . The 3-month protocol glomerular filtration rate of 42 ml/min per 1.73 m<sup>2</sup> (technetium-99m diethylene-triamine-pentaacetic acid) and protocol biopsy was clear from rejection, SV40 staining but had persistence of tubular crystal deposition (associated with detectable crystalluria).

Over the next 9 months, she developed CMV viremia, reactivation of varicella zoster infection, and recurrent urinary tract infections. Her 1-year protocol biopsy (SCr 136  $\mu\text{mol/l}$ , no detectable crystalluria on polarized light microscopy) showed no evidence of rejection or SV40 staining, but persistently detectable birefringent crystals on the biopsy. These were predominantly distributed in the tubular epithelial cells and interstitium; and associated with significant tubular atrophy and interstitial fibrosis. She also developed a mild facial rash around this time, hence the allopurinol was reduced to 200 mg daily (corresponding oxypurinol level 24 ng/ml) with the introduction of febuxostat 40 mg daily.

The results of the serum creatinine, crystal load, and tissue distribution at time of transplant (indication and protocol) biopsy of both cases 1 and 2 are presented in [Figure 3](#). The biopsies of both patients showed similar pattern: early in the disease course, during maximal DHA excretion and crystal formation, most crystals are seen in the luminal space. On maximal allopurinol (and/or

febuxostat) therapy, there was a progressive decline in the number of crystals seen in the luminal space, with more found in the epithelial layer and interstitial space.

### Case 3

A 23-year-old man of Lebanese descent, who experienced 1 episode of urolithiasis in childhood, presented with oliguric acute kidney injury with SCr 1020  $\mu\text{mol/l}$  (12 months prior with SCr 92  $\mu\text{mol/l}$ ). The patient commenced acute hemodialysis given no reversible factors were identified and the renal biopsy showed global sclerosis in 5 of 17 glomeruli, ischemic changes in the viable glomeruli, and birefringent tubular crystals with associated tubular atrophy and severe interstitial fibrosis. The patient's mother had kept this stone and analysis of this revealed "organic" material. Twenty-four hour urine testing revealed 0.23 g/24 hours proteinuria, no hematuria, and borderline elevated urine oxalate 532  $\mu\text{mol/d}$  (normal < 500  $\mu\text{mol/d}$ ). Primary hyperoxaluria was ruled out (negative genetic testing of *AGXT*, *GRHPR*, and *DHDPSL* genes) and no obvious secondary causes were detected on further clinical interrogation. Unexpectedly, this patient coincidentally had the same surname as Case 2 (but not immediately related) and the pathologist suspected APRT deficiency. The diagnosis was confirmed with low enzyme activity (0.09 nmol/min per mg) and a homozygous genetic mutation was confirmed (*c.188G>A*; *p.Gly63Asp*). Crystalluria also was detected in this patient on polarized light microscopy.

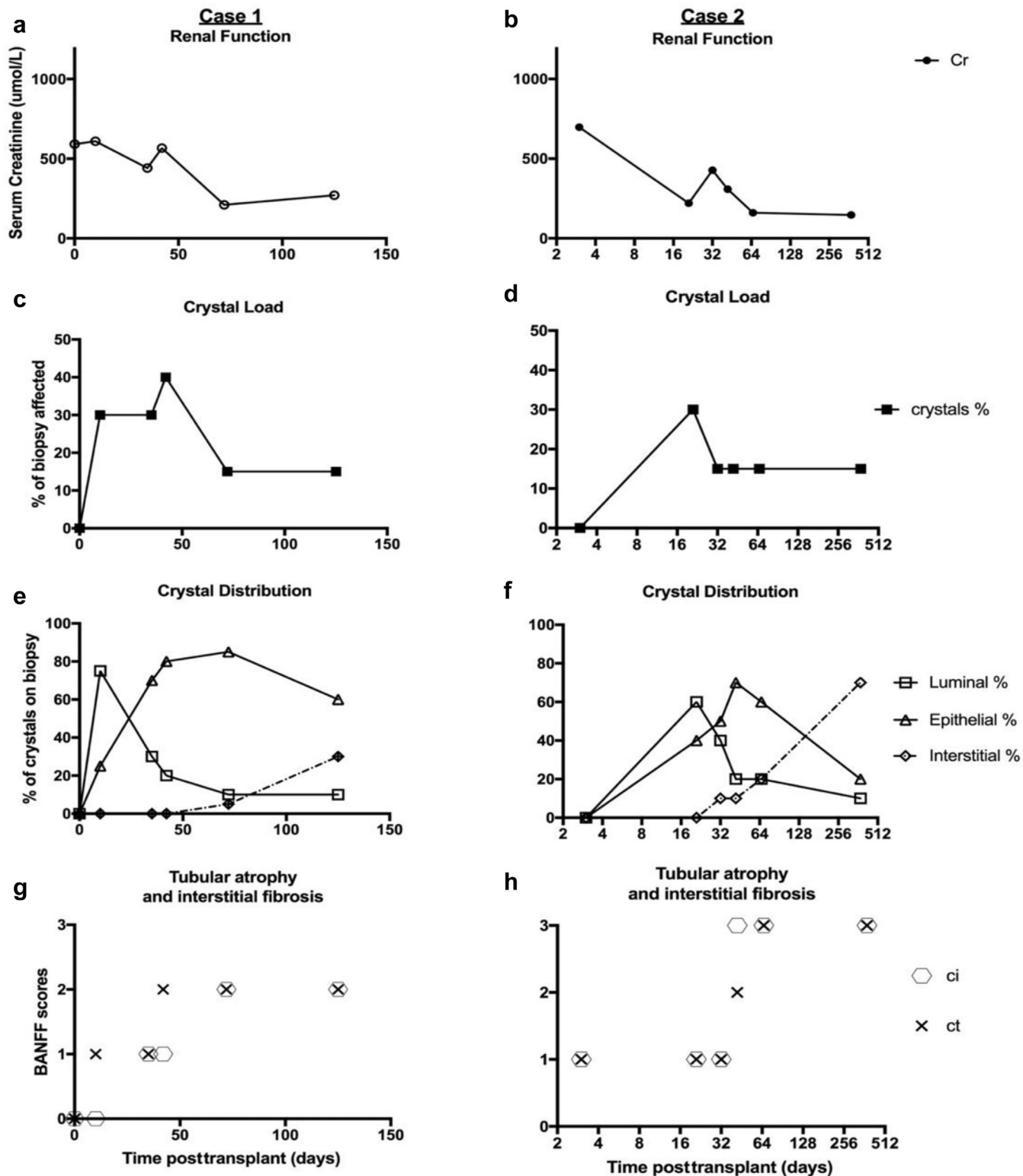
## DISCUSSION

These cases highlight challenging aspects in management of APRT deficiency, particularly given the lack of clinical suspicion, limited access to confirmatory testing, and difficulties in defining target levels of monitoring of disease and response to treatment.

### Diagnostic Issues

The condition was initially misdiagnosed in cases 2 and 3, as chronic interstitial nephritis and oxalate nephropathy. In case 2, the diagnosis was made only after detection of recurrence of crystals in the allograft biopsy; and again, this was initially thought to be oxalate nephropathy. This highlights 2 difficulties with histological diagnosis: (i) native renal biopsies in the late stages of disease may be nonspecific due to long-term scarring; and (ii) it may be misdiagnosed as other forms of crystal nephropathy and requires close examination of the features to differentiate between the causes.

Owing to the rare nature of the disease, there is a low index of clinical suspicion. Clues that should alert the clinician to consider APRT deficiency



**Figure 3.** (a–h) Posttransplant biopsy characteristics (results from all indications and protocol [1-, 3-, and 12-month] biopsies up to July 2018). Case 1 is represented on the left-hand column and case 2 is represented on the right-hand column. Graphs (a) and (b) show the serum creatinine at time of biopsy for case 1 and 2, respectively. Graphs (c) and (d) are the estimated portion of the biopsy section that is affected by crystals and show initial decline, followed by stable levels after allopurinol and/or feboxustat therapy in both patients. Graphs (e) and (f) show the estimated distribution of crystals seen on the renal biopsy: luminal, epithelial, and interstitial compartments. Graphs (g) and (h) demonstrate the tubular atrophy and interstitial fibrosis associated with crystal nephropathy, with severe chronic scores (Banff criteria) seen within the first 12 months posttransplantation.



include histological findings of tubular and/or interstitial deposits of crystalline material, crystalluria, and negative screening (and unresponsiveness to treatment) for other more common causes of crystalline nephropathy.<sup>8</sup>

Access to confirmatory testing also may be a limiting factor. Testing for urinary DHA was not available after the first case (5 years ago). Crystal and stone analysis with infrared mass spectroscopy is also not widely available and would have been useful particularly for case 3, where stone analysis was inconclusive as “organic material.” APRT enzyme activity measured in red cell lysates are usually absent or reduced, but there exist a number of rare pathogenic variants that confer disease but do not lower red cell lysate APRT enzyme activity.<sup>9</sup>

### Targeted Therapy, Dosing, and Monitoring of Symptomatic Individuals

Cornerstone of therapy is to reduce systemic DHA production by reducing purine intake (although most production is via salvage pathway); and inhibition of xanthine oxidase (or xanthine dehydrogenase) with allopurinol or febuxostat (a nonpurine selective inhibitor).

There currently is no effective intervention for removal of DHA metabolite, or increasing its urinary solubility. Dialysis is ineffective in preventing DHA, as it is usually protein bound, and any removal on dialysis would be unable to keep up with the high rate of production given the ubiquitous nature of the purine salvage pathway.

The dosing of allopurinol is not straightforward. High doses of allopurinol<sup>2,4,8,S1</sup> (up to 600 mg) and febuxostat (80 mg)<sup>6</sup> have been required to achieve effective inhibition of DHA crystalluria. Icelandic nephrologists at Landspítali Hospital (who also run the Rare Stone Group Consortium APRT registry) also have used a combination of high-dose 800 mg allopurinol and 80 mg febuxostat in some cases. These doses are much higher than the recommended dose for patients with significant renal impairment or on dialysis, often leading to concerns of allopurinol hypersensitivity or drug reaction with eosinophilia and systemic symptoms. This limitation also applies in the use of febuxostat, although there have been examples of febuxostat being safely used in patients with chronic kidney disease<sup>S5</sup> stage 5 (up to 80 mg daily)<sup>S2–S4</sup> and transplant patients in the management of gout. With these concerns in mind, close monitoring is required for high-dose therapy of either agent, with particular attention to drug reaction with eosinophilia and systemic symptoms/rash, liver dysfunction, or gastrointestinal side effects.

Oxypurinol is the active metabolite of allopurinol and is renally excreted (minimal excretion when creatinine clearance is <10 ml/min, but dialyzable). Oxypurinol levels have been used to help guide the management of gout (recommended trough levels 5–10 mg), but no target levels exist for APRT deficiency.<sup>S6,S7</sup>

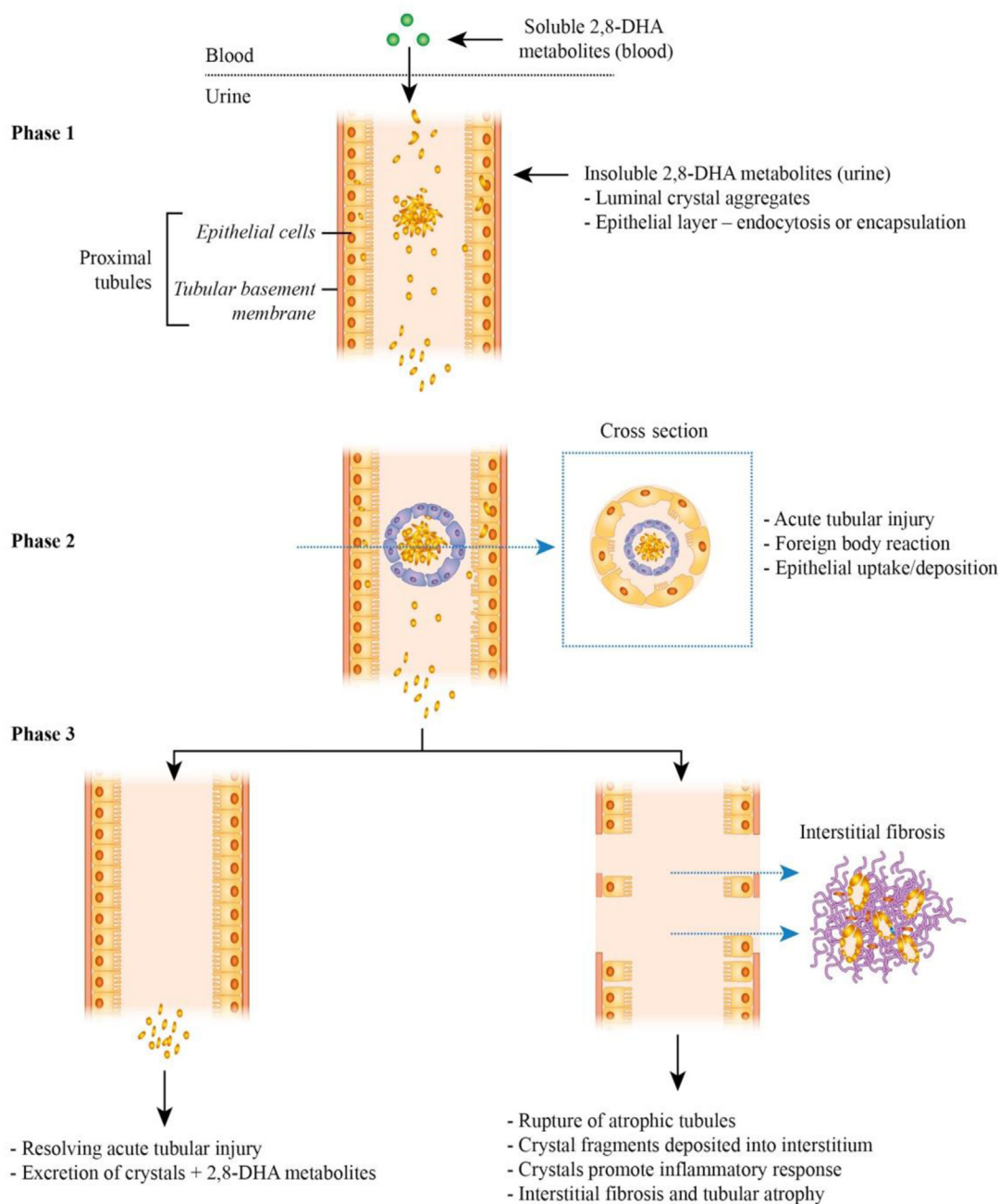
We believe this can be a useful measure to assess therapeutic dosing in future patients, particularly to account for variability with compliance, absorption, metabolism, and renal function rather than a target or weight-based allopurinol dose alone. We measured oxypurinol levels in both transplant patients and found high levels in both despite the different doses: case 1 on 600 mg daily with trough levels 21 to 32 mg/l; and case 2 on 300 mg daily with trough levels above 30 mg/l; the maximum allopurinol dose in both patients was limited by diarrhea. Both patients described mild, erythematous, nonpruritic, nonpalpable facial rash while on long-term therapy. Case 1 was treated for rosacea without change in therapy otherwise; and in case 2, the mild rash resolved with small reduction of allopurinol therapy.

Histological analysis on renal biopsy is the gold standard to assess therapeutic response, although this is limited by the invasiveness, sample error, and the kinetics of crystal formation (new crystal deposition vs. excretion/removal of existing crystals).

Urine microscopy and DHA metabolites are the only noninvasive methods to monitor therapy. Absence of crystals under conventional and polarized microscopy (and if possible, confirmation with infrared microscopy) has been used as a marker for adequate therapy. Measurement of urine DHA metabolites is an attractive option, as it is more sensitive (before formation of crystals) and can be used with allopurinol or febuxostat (no therapeutic level monitoring), but this is measured only through select laboratories. A recent study of 10 patients with APRT deficiency demonstrated marked reduction of urine DHA (24-hour sample and DHA: creatinine ratio) when treated with allopurinol or febuxostat and will be a promising area once validated and more accessible.<sup>S8</sup> The same group is also conducting research into measurement of DHA metabolites in blood, which will be useful in the setting of anuric patients. Uric acid levels are not useful for APRT deficiency (urate levels < 0.25 mmol/l in our patients).

### Issues in Renal Transplantation

Recurrence of disease after transplantation is a major issue, and there have been relatively poor outcomes reported to date for patients with APRT deficiency. In the largest case series (by Zaidan *et al.*<sup>4</sup>) involving 9 patients with renal transplantation, the median delay to diagnosis was 5 weeks after transplantation; and



**Figure 4.** Proposed natural history and kinetics of 2,8-dihydroxyadenine (DHA) crystal deposition in the kidney in adenine phosphoribosyltransferase (APRT) deficiency. The 2,8-DHA is soluble in the systemic circulation, but crystallizes in the urine. Phase 1: these crystals can either form spherical aggregates in the lumen of the proximal tubules (leading to obstruction) or be incorporated into the epithelial layer. Phase 2: these crystals induce (and sustain) a proinflammatory environment, leading to a foreign body reaction and tubular injury. Phase 3: these crystals are either excreted in the urine or are deposited into the interstitial space due to disruption to the tubular basement membrane from chronic inflammation and/or tubular rupture. Interstitial crystals continue to provoke a proinflammatory environment, leading to interstitial infiltration followed by chronic fibrosis.

despite allopurinol or feboxustat therapy, 7 of 9 patients developed chronic allograft nephropathy or graft loss. One case series (by Nasr *et al.*<sup>8</sup>) reported a patient treated with combination prednisolone and allopurinol (400 mg/d) before transplantation, with no evidence of recurrence, but unfortunately died with multiorgan failure from unrelated reasons; and another patient treated with allopurinol (200 mg/d) who suffered from recurrence of disease.

As described earlier, the optimal dosing of allopurinol or feboxustat is unclear and clearly poses a challenge in future renal transplant candidates given the risk of early recurrence, chronic graft dysfunction, and loss. Although our patient in case 1 was already on allopurinol before transplantation, he was probably underdosed for his weight; and likely needed additional postdialysis dosing, given the active metabolite (oxypurinol) was dialyzable.



In the early posttransplant setting, there is high risk of acute graft dysfunction from a “dumping” phenomenon, with vast amounts of accumulated systemic DHA excreted into the urine by the new allograft kidney. The risk of tubular crystal formation is higher in the setting of oliguric or low flow states; and both our patients were found to have hypocitraturia.

Early crystal formation and deposition is associated with acute tubular injury, tubular obstruction, foreign body reaction, and tubulitis. It was difficult to distinguish if inflammation on the biopsies was due to crystalline disease or if there was concurrent early or “borderline rejection” (tubulitis and interstitial infiltrates but not meeting Banff Criteria for type 1A rejection). Given they both suffered from delayed graft function, inflammation on the early biopsies was treated with intravenous methylprednisolone, and 1 patient progressed to develop unequivocal Banff grade 2A rejection. This dilemma is not a benign problem, and the clinical assessment will need to be individualized to balance the risk of long-term adverse graft outcomes of borderline/subclinical rejection or tubulitis secondary to crystalline disease versus the well-established complications of overimmunosuppression.<sup>S10,S11</sup> Both patients suffered infectious complications: case 1 with invasive CMV; and case 2 with BK nephropathy, varicella zoster reactivation, CMV viremia, and recurrent urinary tract infections.

### Disease Course and Kinetics

We reviewed the posttransplant biopsies of our patients and found that early in the disease course, crystals were almost exclusively seen in the proximal tubules. With the initiation of allopurinol therapy, there was at least no further increase in overall crystal burden, with very slow, small decrement over several months for both cases.

Sequential biopsies in both our transplant patients (on maximal tolerated allopurinol) showed changes to the distribution of crystal load. We hypothesize based on the results presented in [Figures 2a and b](#) and [3e and f](#), following early luminal deposition, the crystals are then also incorporated into the tubular epithelial layer by either endocytosis, or encapsulation (formation of new layer of epithelial cells).<sup>S9</sup>

This is then followed by atrophy or rupture of the tubular basement membrane and deposition of crystals into the interstitial compartment ([Figure 4](#)). Interstitial crystal deposition sustains an ongoing inflammatory response, leading to chronic tubular atrophy and interstitial fibrosis and is an important contributor to the progressive chronic tubular and interstitial Banff scores in our patients ([Figure 3g and h](#)).<sup>S9</sup>

### Screening and Genetic Counseling

Genetic testing in family members of a patient diagnosed with APRT deficiency relies on pathogenic variants being found in the proband. The large majority of probands will have mutations detectable by sequencing, although rare individuals may have pathogenic deletions that may be missed by Sanger sequencing or exome capture–based techniques. Diagnosis in other family members, particularly at-risk siblings, may then proceed using the known mutations.

Alternatively, APRT enzyme activity or urinary purine metabolite analysis might be more appropriate dependent on cost and availability. Genetic counseling should be offered to family members.

Management of patients with asymptomatic APRT deficiency found on either genetic or enzymatic testing is unclear. There is a risk of silent disease, as some cases manifest in childhood,<sup>2,S12</sup> whereas some are detected only when patients are found to have late-stage chronic kidney disease in adulthood. It is tempting to treat all patients regardless of symptoms, particularly because allopurinol is a relatively inexpensive drug, but it may be useful to consider renal function and urinary screening (crystalluria or DHA metabolites) to decide whether long-term exposure to high-dose allopurinol is warranted.

### CONCLUSION

APRT deficiency is an important differential to consider in patients with undetermined crystal nephropathy or nephrolithiasis. It is potentially reversible, but the current treatment strategies are far from satisfactory, and this has implications on long-term graft survival in transplant recipients.

### DISCLOSURE

All the authors declared no competing interests.

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### SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

[Supplementary Methods.](#)

[Supplementary References.](#)

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## Effect of a Somatostatin Analogue on the Vasopressin Pathway in Patients With ADPKD



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**A**utosomal dominant polycystic kidney disease (ADPKD) is characterized by high activity of adenylyl cyclase (AC) in renal tubular cells, which stimulates the conversion of adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP). This results in high intracellular cAMP levels, which lead to aberrant renal tubular epithelial cell proliferation and chloride-driven fluid excretion in the kidney, causing cyst formation and growth. Ultimately these processes lead to kidney failure, with a need for renal replacement therapy such as dialysis or renal transplantation.

The vasopressin V2 receptor antagonist tolvaptan has the ability to inhibit the activity of AC and to lower cAMP levels. Tolvaptan can therefore attenuate kidney growth and the rate of renal function decline.

However, the effect of tolvaptan is limited to the kidney, and its aquaretic side effects hamper widespread clinical use. Therefore there is still an unmet need for new therapies to slow disease progression in ADPKD. In this respect, somatostatin analogues are of interest, as somatostatin analogues also have the ability to lower intracellular cAMP levels by inhibiting the activity of AC in kidney as well as liver tissue. These drugs decrease the growth rates of liver and kidney volume in ADPKD.<sup>1–5</sup>

Because both drugs lower cAMP levels by inhibiting the activity of AC, it may be that there is a pharmacodynamic interaction between somatostatin analogues and tolvaptan. Interestingly, older experimental studies have suggested involvement of somatostatin in renal water handling, causing either a