Shining a light on an unusual case of CKD.

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A 65 year old man of African (?) origin was referred to the renal clinic for investigation of deteriorating renal function. His eGFR had fallen from 37ml/min to 23ml/min (creatinine 292 µmol/l) over 12 months. He had a past medical history of chronic back pain, Bell 's palsy, hypertension and gout. He was noted to have a family history of chronic kidney disease (CKD) in that his daughter had recently been diagnosed with renal sarcoidosis. Clinical examination was unremarkable. Urinalysis revealed only trace proteinuria and no haematuria. A renal ultrasound revealed echogenic 10cm kidneys bilaterally with no evidence of obstruction. A screen for infection and immunologically-mediated renal disease, as well as for multiple myeloma, was negative. A renal biopsy was performed to determine the cause of his CKD. Histology under normal and polarised light microscopy is shown in figure 1.

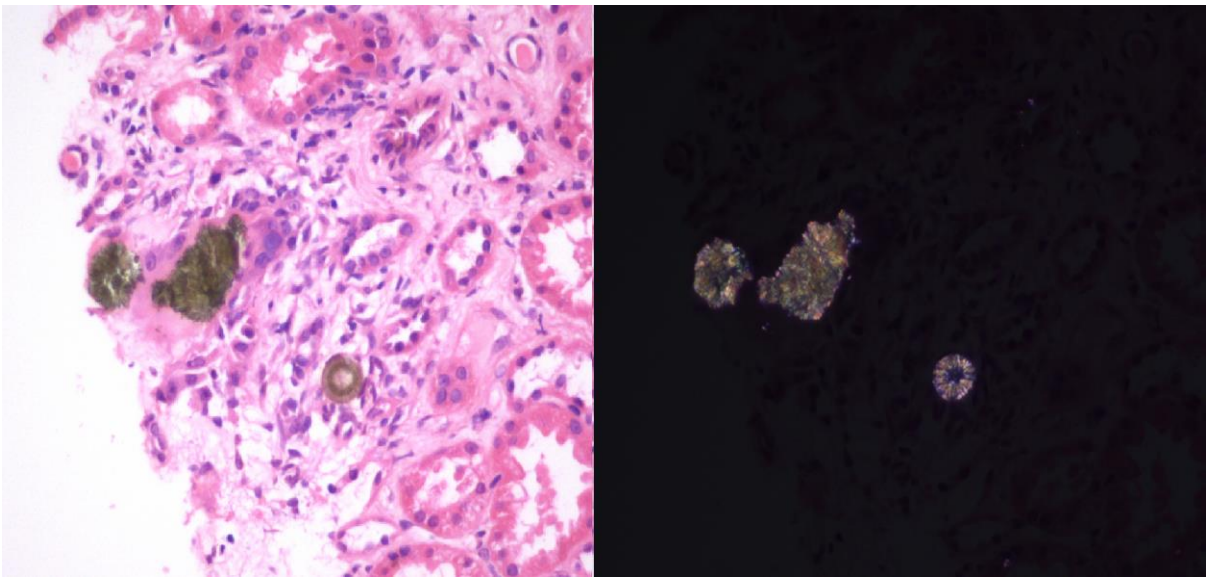

Figure 1. x20 magnification of renal biopsy under normal and polarised light.

What is the diagnosis?

Answer: Adenine phosphoribosyltransferase deficiency with crystalline nephropathy.

The renal biopsy demonstrated green/brown crystalline material within tubular lumina and epithelial cells eliciting a multinucleate giant cell reaction. On polarised light microscopy the crystals were clearly refractile. Chronic parenchymal damage with a chronic inflammatory cell interstitial infiltrate was also seen.

Given the characteristic appearance of the 2,8-dihydroxyadenine (DHA) crystals, a diagnosis of adenine phosphoribosyltransferase (APRT) deficiency was suspected, and subsequently confirmed on laboratory testing with complete absence of red cell APRT enzyme activity.

APRT is a purine salvage enzyme that recycles 5'-adenosine monophosphate (AMP) from adenine. In APRT deficiency, adenine is instead converted via xanthine dehydrogenase (also known as xanthine oxidase) to DHA (Figure 2). The latter is cleared by the kidney but remains largely insoluble in urine, precipitating in the renal tubules causing both an obstructive nephropathy and crystalline nephritis (1).

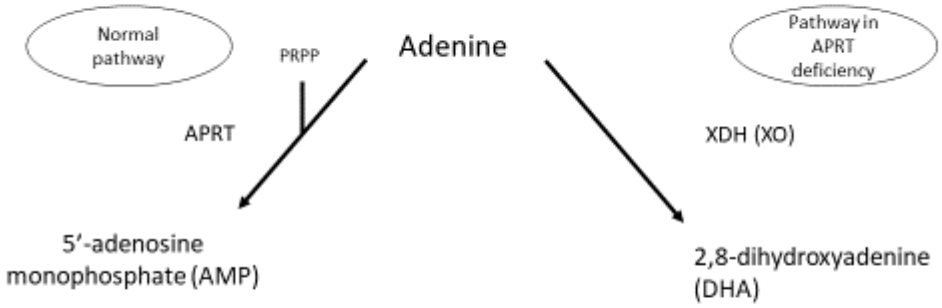

Figure 2. Simplified adenine metabolism pathway. Adenine cannot be converted to adenosine in humans and so the only remaining metabolic pathway is conversion to the insoluble 2,8-dihydroxyadenine by xanthine dehydrogenase (formerly known as xanthine oxidase). Adapted from Bollee et al, American Journal of Nephrology (2010).

APRT deficiency is an autosomal recessive condition manifesting with very low, or absent enzyme activity. Classically reported to cause kidney stones in infants, the condition is increasingly being diagnosed in adults. Clinical manifestations can occur at any age and are due to urolithiasis or 'DHA nephropathy'. Whilst genetic in origin, factors such fluid intake and purine consumption are thought to account for the phenotypic variability of the disease. The quoted prevalence of 1 in 50,000-100,000 people is likely an underestimate due to low awareness of the condition and its often indolent presentation.

Diagnosis of APRT deficiency can be made by identifying DHA in kidney stones or crystals in urine. The diagnosis is then confirmed by measuring red cell APRT enzyme activity at specialist centres. Renal biopsy is not needed for diagnosis of this condition, but occasionally, as in our case, is the means by which the condition is identified. Due to the heterogeneity of mutations identified, genetic analysis is not diagnostic.

Untreated, APRT deficiency can lead to end-stage kidney disease which can recur in transplanted kidneys (2). Whilst no cure exists, it is easily treatable. Allopurinol, by inhibiting xanthine dehydrogenase, prevents the conversion of adenine to DHA. Following treatment with allopurinol at 300mg daily, our patient's eGFR at six months improved to 30ml/min (creatinine 230 μmol/l). Whilst rare, APRT deficiency is easily treatable and worth considering especially when faced with urolithiasis with unknown stone type or any CKD of unknown origin, especially with bland urine sediment.

References

1. Bollee G, Harambat J, Bensman A, Knebelmann B, Daudon M, Ceballos-Picot I. Adenine Phosphoribosyltransferase Deficiency. Clin J Am Soc Nephrol [Internet]. American Society of Nephrology; 2012 Sep 1 [cited 2017 Jul 22];7(9):1521–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22700886

2. Bollée G, Dollinger C, Boutaud L, Guillemot D, Bensman A, Harambat J, et al. Phenotype and genotype characterization of adenine phosphoribosyltransferase deficiency. J Am Soc Nephrol [Internet]. American Society of Nephrology; 2010 Apr 1 [cited 2017 Jul 22];21(4):679–88. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20150536

3. APRT Deficiency Clinician Information | Rare Renal [Internet]. [cited 2017 Jul 23]. Available from: http://rarerenal.org/clinician-information/aprt-deficiency-clinician-information/