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Case Report

Two birds one stone-two rare cases of adenine phosphoribosyl transferase deficiency

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ABSTRACT

Complete adenine phosphoribosyl transferase (APRT) deficiency is a rare inherited metabolic disorder that leads to the formation and hyperexcretion of 2,8-dihydroxyadenine (DHA) into urine. We had a 52-year-old male with Hypertension for 18 months, presented for routine evaluation and was found to have creatinine of 4.29 mg/dl. His urine analysis was done which showed no proteinuria or urinary sediments. His USG done demonstrated normal sized kidneys with mildly increased echogenicities. He underwent a renal Biopsy for etiology determination. Similarly, we had another case of a 54-year-old female with no comorbidities who was identified to have chronic kidney disease in 2018 with a baseline creatinine of 2 mg/dl came with uremic symptoms and history of NSAID intake in June 2019. Her creatinine peaked to 7.9 mg/dl. Urine analysis displayed 1+ proteinuria with no active sediments. Her USG of the kidneys showed normal kidneys with increased echogenicities. She underwent renal biopsy for etiology determination. Biopsy of case 1 showed chronic interstitial nephritis and case 2 showed acute interstitial nephritis. Both biopsies showed deposition of 2,8-dihydroxyadenine crystals. Genetic analysis of both cases showed an exon mutation in chromosome 16.

Keywords: Stones, APRT, Genetic disease

INTRODUCTION

Adenine phosphoribosyltransferase (APRT) deficiency is an inherited metabolic disorder that leads to the excessive formation and excretion of 2,8-dihydroxyadenine (DHA) in the urine.[1]

DHA has poor solubility and it's precipitation leads to the formation of urinary crystals and stones.[1] The presentation of APRT deficiency can be varied in the form of recurrent urolithiasis or nephropathy secondary to crystal precipitation into renal parenchyma (DHA nephropathy). APRT diagnosis requires stone or crystal analysis, genetic analysis and APRT activity measurement which helps to make the diagnosis easy to confirm when APRT deficiency is suspected.[2] However, the disease can present at any age, and the variability of symptoms can present a diagnostic challenge to many physicians. The early recognition and treatment of APRT deficiency are of crucial importance for preventing irreversible loss of renal function.

CASE REPORT

Case 1

A 52-year-old gentleman who was diagnosed with hypertension came to the outpatient department for a routine evaluation, his renal functions showed a creatinine of 4.2 mg/dl. On examination, he had no pedal edema, no history of haematuria or frothy urine. His urine analysis done showed no proteinuria and no active sediments. He did not have a baseline creatinine.

Ultrasound done showed normal sized kidneys and mildly increased echogenicities. It seemed like an interstitial pathology and in order to identify the etiology a renal biopsy was done which showed chronic interstitial

nephritis with deposition of 2,8 DHA crystals. He was started on Febuxostat and reduce intake of purine rich food; he is currently stable with a creatinine in the range of 3-4 mg/dl.

Genetic analysis of case 1 done showed a novel mutation of autosomal recessive homozygous start loss in exon 1 of APRT gene on chromosome 16.

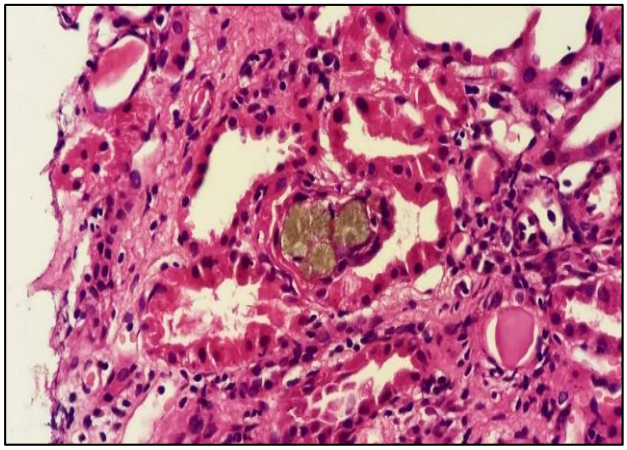

Figure 1: Light microscopy of 2,8-DHA crystals.

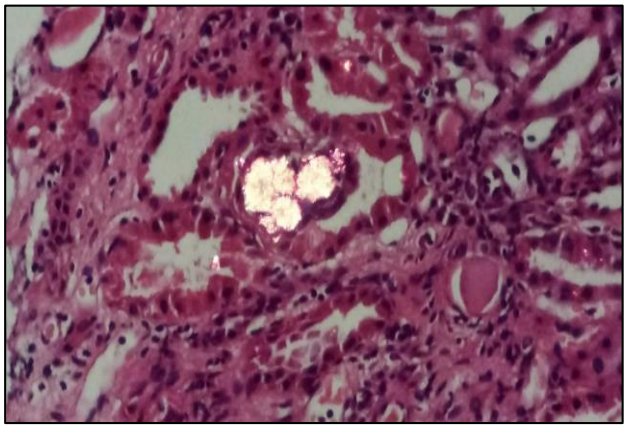

Figure 2: Polarised microscopy showing 2,8- DHA crystals.

Case 2

A 54 year old female with no comorbidities was identified to have Chronic kidney disease in 2018 with a baseline creatinine of 2 mg/dl came with uremic symptoms and history of NSAID intake in June 2019. Her creatinine peaked to 7.9 mg/dl. Urine analysis displayed 1+ proteinuria with no active sediments. Her USG of the kidneys showed normal kidneys with increased echogenicities. She underwent Renal biopsy for etiology determination which showed Acute interstitial nephritis with deposition of 2,8 DHA crystals. Patient was initiated on hemodialysis, and currently continues to be dialysis dependant. Genetic analysis for case 2 showed a mutation of autosomal recessive homozygous in frame deletion in exon 5 of APRT gene on chromosome 16.

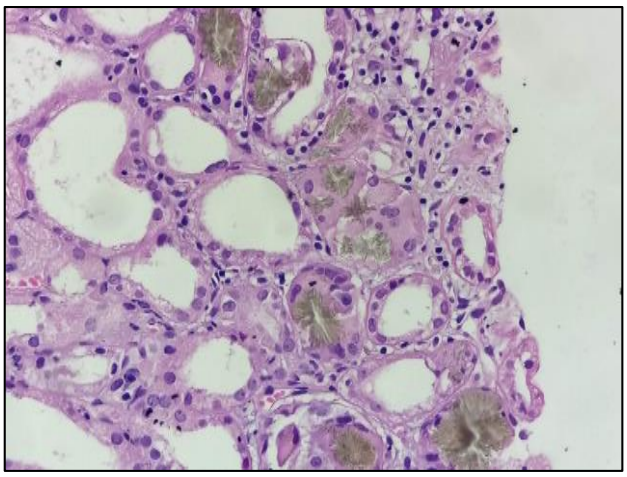

Figure 3: Light microscopy of 2,8- DHA crystals.

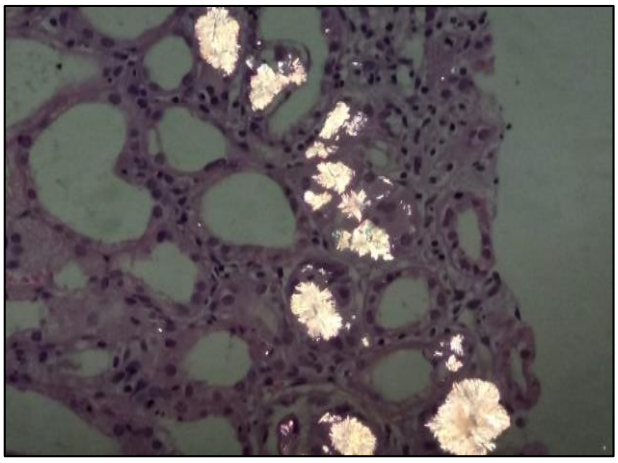

Figure 4: Polarised microscopy of 2,8-DHA crystals.

DISCUSSION

APRT deficiency is a rare inherited metabolic disorder that excess formation and excretion of 2,8-dihydroxyadenine (DHA) into urine[1]. The APRT gene is located on chromosome 16q24 consisting 2.8 kb of DNA, contains five exons, and has a coding region of 540 bp with autosomal recessive inheritence.[2,3] APRT deficiency is a very rare disease, with most cases published from Japan, however its worldwide prevalence remains largely unknown. [4]

The APRT enzyme is constitutively expressed. It can be detected in all tissues and provides the only pathway for the metabolic salvage of adenine resulting from polyamine biosynthesis and dietary sources.[5] APRT is involved in the process of formation of 59-adenosine monophosphate and inorganic pyrophosphate from adenine and 5-phosphoribosyl-1- pyrophosphate, allowing adenine to be detected only at low levels in blood and urine. Those lacking functional APRT, adenine is converted to 8-hydroxyadenine, which is further metabolized to DHA by xanthine dehydrogenase (XDH), previously known as xanthine oxidase .[6,7] DHA has a

high renal clearance, which may involve both filtration and tubular secretion. APRT deficiency therefore results in high urinary excretion of DHA. DHA is extremely insoluble in urine and forms crystals, which lead to formation of stones by the process of nucleation, aggregation and growth or precipitate in renal parenchyma, causing crystalline nephropathy.[8,9]

Complete APRT deficiency often poses a diagnostic challenge not only because of variability of symptoms and age of onset but also lack of awareness. The disease can present with two types of clinical manifestations, which may occur together or separately: urolithiasis and crystalline nephropathy.[10] The term "DHA nephropathy" is used for the crystalline nephropathy secondary to DHA precipitation. DHA nephropathy may have an acute presentation with Acute kidney injury developing over a few days or more frequently, develop insidiously and cause progressive decline of renal function over several years like chronic interstitial nephritis.[5]

Unfortunately, the diagnosis is often delayed by years after the onset of symptoms, and most patients would have already developed irreversible renal failure when adequate treatment is implemented. There is a crucial need for earlier recognition and better management of APRT deficiency. Studies in European and Japanese populations have highlighted that APRT deficiency can present at any age. The age at diagnosis varies from infancy to older than 70 years.[11]

The diagnosis of APRT deficiency is primarily based on the identification of DHA, either by examination of crystals in urine or by stone analysis. Stones should be analyzed if available by the combination of morphologic examination under stereomicroscope.[12,13] Renal biopsy usually shows severe tubular injury and precipitation of crystals within tubular lumen and in renal interstitium. The crystals may lack the typical features of DHA and their presence in renal parenchyma should never be dismissed. The best method is to characterize crystals in renal biopsy using polarizing microscopy.[1,12] The mutations involved may be determined by sequencing of PCR-amplified DNA, which can be readily performed given the small size of APRT gene.[6]

APRT activity cannot be increased by any therapy. Treatment of APRT deficiency relies on allopurinol therapy, which acts by blocking Xanthine dehydrogenase.[14] In patients with DHA nephropathy, allopurinol therapy usually allows renal function to stabilize or improve and prevents recurrence after renal transplantation. The possibility of renal function recovery largely depends on the degree of acute tubular necrosis and chronic tubulointerstitial changes when treatment is initiated. All individuals with complete APRT deficiency, even asymptomatic, should be treated by allopurinol, given the risk for acute or insidious DHA nephropathy. Allopurinol dosage is 200-300 mg/d in adults and 5-10 mg/kg per day in children.[14]

Febuxostat, another XDH inhibitor, is an alternative in allopurinol-intolerant patients. Dietary modifications in the form of high fluid intake (at least 2.5 L of water per day in adults) and avoidance of purine-rich food should be advised. Alkalization does not have to be recommended because DHA remains very insoluble at pH values below 8.5. [14-16] One should also be cautious during transplantation as the disease can recur on transplantation and this is why determination of native kidney disease is important. [15,16]

CONCLUSION

APRT deficiency represents a unique example of a disease that potentially leads to renal failure but can be easily treated by taking a pill each day. Physicians should therefore leave no stone unturned when it comes to caring for patients with urolithiasis or renal disease. There is a need to make diagnostic tools, especially APRT activity assay, more available.

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