Dihydroxyadenine stone with adenine phosphoribosyltransferase deficiency: A case report

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ABSTRACT

Adenine phosphoribosyltransferase (APRT) deficiency is a rare autosomal recessive error of purine metabolism resulting in the generation of 2,8-dihydroxyadenine (DHA), a highly insoluble metabolite of adenine, which can cause radiolucent urolithiasis. This is the second case of DHA stone being reported in India and the first case in India to document the mutation of the APRT gene on blood DNA analysis.

INTRODUCTION

Adenine phosphoribosyltransferase (APRT) deficiency is a rare autosomal recessive disorder leading to the formation of 2,8-dihydroxyadenine (DHA) stone. Various diagnostic modalities include identification of Maltese cross pattern in DHA crystals in urine, stone analysis, kidney biopsy, and genetic analysis. Early diagnosis and timely institution of pharmacologic (allopurinol or febuxostat) treatment can significantly reduce or prevent adverse renal outcomes in patients.

CASE REPORT

A 2-year-old female child born to a consanguineously married couple presented to us with a history of blood-stained undergarments, gross hematuria, and right flank pain. She had the previous history of one episode of febrile urinary tract infection which was treated with antibiotics elsewhere and had no family history of urolithiasis. Clinical examination was normal. Her blood investigations were as follows: hemoglobin 10.4 g/dl, total leukocyte count 15370 cells/cumm, serum creatinine 0.4 mg/dl, corrected serum calcium 9.3 mg/dl, serum uric acid 2.9 mg/dl, serum potassium 5.0 mEq/L, and serum bicarbonate 23.1 mEq/L. Urine analysis showed pH 6.5, 6–8 red blood cell, and 1–2 white blood cell. Urine culture showed no growth.

Ultrasound kidneys, ureters, and bladder (KUB) revealed 5.2 mm lower calyceal renal calculus, 6.8 mm × 3.8 mm right pelviureteric junction calculus with right moderate hydronephrosis.

In view of recurrent severe pain, she underwent right mini-percutaneous nephrolithotomy. Multiple yellow colored tiny fragmented stone were seen in all the calyces, which were siphoned out. The larger fragment at the PUJ was retrieved with a basket. Postoperatively, she had a mild drop in oxygen saturation, which was managed with oxygen supplementation for 4 h.

Stone analysis by Fourier transform infrared spectroscopy showed a composition of 100% of 2,8-DHA. At the first follow-up visit, the child was advised further workup but was lost to follow-up for 5 months. She subsequently presented to us after 5 months when she noticed gross hematuria again. On ultrasound KUB, she was found to have right 3.6 mm renal calculus and 4.5 mm bladder calculus.

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A repeat urine sample was analyzed. Light microscopy of the urine sediment showed 2,8-DHA crystals in urine which are brownish with a darker outline and spicules radiating from the center. Polarization of the 2, 8-DHA crystals revealed characteristic Maltese cross pattern [Figure 1].

She was started on allopurinol 10 mg/kg/day and increased daily intake of water. A subsequent ultrasound KUB showed no bladder calculus but persistence of a small 3 mm right renal calculus.

Blood was analyzed for mutation screening of the APRT gene which confirmed the location of the mutation at Exon 1 with “c.2T>C” variant. With a follow-up of 18 months on allopurinol, the child continues to be asymptomatic with a 2 mm right renal calculus. The younger sibling was evaluated and found to have no DHA crystals on urine polar microscopy.

**DISCUSSION**

APRT deficiency was first described in 1968 by Kelley et al. The disorder has been described in all ethnic groups, but the majority of reported cases are from Japan, France, and Iceland. The only case of DHA stone from India was reported by Sreejith et al. in 2009 based only on stone analysis.

The human APRT gene is located on chromosome 16q24 and contains 5 exons encoding an 180 amino acid protein. Most of the mutations are single base changes and small deletions. A missense mutation in exon 5 (p.Thr136Met) affects approximately 70% of Japanese patients. The most common mutations in other ethnic groups are a T insertion at the splice donor site of intron 4 (c.IVS4 + 2insT) and a missense mutation in exon 3 p.Asp65Val, which accounts for all cases of APRT deficiency in Iceland. The location of the mutation in this patient was at Exon 1 with “c.2T>C” variant and this variant was not found on Biobase, NCBI snp database, ClinVar, and ExAC databases.

Allopurinol (10 mg/kg/day) and adequate fluid intake are the mainstay of the treatment. Allopurinol can result in resolution of kidney stones and improvement of kidney function in patients with advanced renal failure. Dietary purine restriction in patients receiving drug treatment has not been proven. Urinary alkalinization will not help since DHA is highly insoluble at any physiological pH. Febuxostat is an alternative option for patients allergic/intolerant to allopurinol, although the evidence of its efficacy is still unavailable.

Surgical management of DHA stones is similar to other urinary stone types, and DHA stones can generally be managed by shock wave lithotripsy. Renal transplantation, coupled with allopurinol or febuxostat therapy, is the treatment of choice for patients in who end-stage renal disease (ESRD) develops. ESRD has been reported to be the presenting feature in approximately 15% of adults, and also recurrence has been noted in transplant patients.

This is the first case from India where all three diagnostic parameters (stone analysis, urine DHA crystals having Maltese cross pattern, and blood genetic analysis) were confirmed to diagnose APRT deficiency.

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