Abstract

Adenine phosphoribosyltransferase deficiency is a rare autosomal recessive disorder of uric acid metabolism that leads to formation and excretion of 2,8-dihydroxyadenine into urine. The low solubility of 2,8-dihydroxyadenine results in precipitation and formation of urinary crystals and renal stones. Patients with this disorder usually have recurrent nephrolithiasis and can develop nephropathy secondary to crystal precipitation in the renal parenchyma. The disease is most often underdiagnosed and can recur in renal transplant, causing graft failure. Lack of specific clinical manifestations, chemical and radiologic features identical to those shown with uric acid stones, and lack of awareness among clinicians are among the causes for the underdiagnoses of this treatable disease. Allopurinol, a xanthine dehydrogenase inhibitor, is the mainstay of treatment, supported by high fluid intake and dietary modifications. The possibility of adenine phosphoribosyl transferase deficiency should be considered in all cases of urolithiasis in children, patients with recurrent urolithiasis, and patients with urolithiasis associated with renal failure of unknown cause, including patients with end-stage renal disease and renal transplant recipients. Here, we report a case of a 41-year-old female patient who had a late diagnosis of 2,8-dihydroxyadenine nephropathy-induced end-stage renal disease, made on the native nephrectomy that accompanied the renal transplant, and who had a timely intervention that prevented recurrence in the graft.

Key words: Adenine phosphoribosyl transferase deficiency, Kidney, Stones

Introduction

Adenine phosphoribosyltransferase (APRT) deficiency is a rare, inherited autosomal recessive metabolic disorder that leads to the formation and hyper-excretion of 2,8-dihydroxyadenine (DHA) into urine.1,2 The low solubility of DHA results in precipitation and formation of urinary crystals and kidney stones that manifest as recurrent urolithiasis or nephropathy secondary to crystal precipitation into renal parenchyma (DHA nephropathy).3-5 2,8-Dihydroxyadenine crystalline nephropathy can recur in the renal allograft in the absence of prophylactic treatment, which leads to allograft loss in more than 25% of cases.5,9

Adenine phosphoribosyltransferase deficiency is a potentially severe condition that tends to be overlooked, especially in adults. Lack of awareness about this entity and misidentification of these stones as uric acid stones on routine analysis are among the causes for a delayed diagnosis. Herein, we report the case of a 41-year-old female patient who had a late diagnosis of DHA nephropathy-induced end-stage renal disease, made on the native nephrectomy that accompanied the renal transplant, and who had prompt prophylactic treatment, which prevented recurrence in the graft.

Case Report

A 41-year-old female patient was admitted to the nephrology center for a renal transplant following end-stage renal disease due to recurrent nephrolithiasis. Her past history was significant for recurrent nephrolithiasis and urinary tract infections since childhood. She had undergone left nephrectomy 18 years previously for infected nonfunctioning kidney, histopathology of which was not available. The nephroliths had been reported as calcium oxalate and urate stones by standard analyses. She had also then
undergone pyeloplasty of her right kidney. Other additional events were hysterectomy for uterine fibroids 2 years previously and left lower limb deep vein thrombosis 1 year previously. Her mother and 1 sister had frequent urinary stones, but they had had no significant renal problems.

In 2014, she underwent living-donor renal transplant from her sister with 3 mismatches and negative crossmatch along with right native nephrectomy (Figure 1a). Her postoperative period was remarkable for an episode of cardiac tamponade for which urgent pericardiocentesis and drainage of pericardial fluid were done. The patient received standard immunosuppression: induction with basiliximab and maintenance with prednisolone, mycophenolate sodium, and cyclosporine. Histopathology of the right native nephrectomy was also conducted, showing chronic tubulointerstitial nephritis with abundant brown crystals (Figure 1b and 1c), which were present in the tubular lumina and tubular cell cytoplasm and focally within the interstitium, associated with foreign-body type giant cells (Figure 1d).

The examined crystals were arranged as rods, irregular shapes, annular formations of striated crystals, and fan-like shapes (Figure 2a and 2b). The crystals appeared black on silver stain (Figure 2c) and showed absence of calcium on von Kossa stain (Figure 2d). They were strongly birefringent when examined under polarized light. The possibility of DHA crystalline nephropathy was raised. However, urine microscopic examination after renal transplant did not show any evidence of crystalluria.

On further interrogation, it was found that the patient had preserved the renal stones that she passed in urine earlier, and these were evaluated. Naked eye examination revealed several pieces of irregularly shaped, light brown, soft, friable crystals with rough surfaces (Figure 3). A Fourier transform infrared spectroscopy analysis of the stones revealed these to be 100% containing DHA. Due to the lack of resources, APRT enzyme level estimation and a genetic study were not done. The patient was subsequently started on 300 mg/d allopurinol and was monitored for crystalluria. At the last follow-up, she had stable renal function and no evidence of crystalluria.

Figure 1. Chronic Tubulointerstitial Nephritis

(a) Gross specimen of the native nephrectomy. (b and c) Chronic tubulointerstitial nephritis with abundant brown crystals deposition (hematoxylin and eosin stain; ×200 magnification). (d) Chronic tubulointerstitial nephritis, with arrow showing foreign body giant cell reaction to crystals (hematoxylin and eosin stain; ×200 magnification).

Figure 2. Details of Crystals in Patient

(a and b) Different arrangements of crystals as annular formations, rods, and fan-like shapes (hematoxylin and eosin stain; ×400 magnification). (c) Crystals appearing black on silver stain. (d) Absence of calcium within the crystals (von Kossa stain).

Figure 3. Soft, Friable Light Brown Stones With Rough Surface
Discussion

Adenine phosphoribosyltransferase deficiency is a rare hereditary cause of nephrolithiasis, transmitted in an autosomal recessive fashion, with the gene located on chromosome 16q24.1,2 Adenine phosphoribosyltransferase deficiency is often considered a very rare disease, although its worldwide prevalence remains largely unknown. The vast majority of cases are from Japan, France, and Iceland. The prevalence of APRT deficiency is estimated to be 1/27 000 in the Japanese population and between 1/50 000 and 1/100 000 in people who are white.9 Adenine phosphoribosyltransferase is an enzyme in the purine metabolism pathway that converts adenine into adenosine monophosphate. A lack of this enzyme results in accumulation of adenine, which is alternatively converted to DHA by xanthine oxidase. In plasma, DHA is protein bound, but it forms insoluble crystals in urine. Two types of APRT deficiency are recognized based on the level of enzyme activity in cell extracts.10 Adenine phosphoribosyltransferase activity is null in type 1, mostly reported in white individuals, whereas it is about 15% to 30% of the normal activity in type 2, exclusively described in Japanese patients, where it accounts for 70% of cases of APRT deficiency. This classification has no relevance in vivo or in intact cells where enzymatic activity is less than 1% in types 1 and 2. The clinical presentation is similar in both types of deficiencies.10

Although the enzyme deficiency is present at birth, the symptoms related to APRT deficiency may occur from early childhood to the seventh decade of life. The symptoms in homozygous patients range from nephrolithiasis in most cases to chronic renal failure in severe cases, whereas heterozygote patients are generally asymptomatic and usually have normal excretion of DHA and no DHA crystals in their urine, despite these patients having partial APRT deficiency. Extrarenal manifestations have not been reported because of the absence of any systemic deposition of DHA.

Urolithiasis is the most common manifestation of APRT deficiency. The stones are soft and friable with an irregular surface and are characteristically radiolucent. 2,8-Dihydroxyadenine nephropathy causing chronic renal disease represents the second manifestation of APRT deficiency commonly observed in adults but rarely in children. 2,8-Dihydroxyadenine causes renal failure by precipitating in the renal tubules and interstitium. In renal transplant recipients, 2,8-DHA crystals can be detected in the urine within the first few days after transplant, which can cause graft dysfunction. 2,8-Dihydroxyadenine nephropathy can recur after renal transplant and lead to transplant failure in more than 25% of patients, and this occurs in instances where the disease was not recognized before the transplant.7,8 Recurrence of nephrolithiasis has been reported but is less common than in native kidneys.

The diagnosis of APRT deficiency is primarily based on the identification of DHA, either by examination of crystals in urine or by stone analysis. Crystalluria examination by light and polarizing microscopy is a very useful noninvasive and inexpensive tool for the identification of round, reddish-brown DHA crystals with dark outlines, central spicules, and maltese cross-pattern on polarization. Stone analysis done using a combination of stereomicroscope and infrared spectroscopy allows identification of DHA in all cases. Stone analysis using biochemical methods, including colorimetric reaction and thermogravimetric analysis, can incorrectly identify these as uric acid crystals due to their identical chemical reactivity, as occurred in our case.10

Histopathological analyses of DHA crystals on renal biopsy can be difficult as results can be confused with other crystalline deposits such as uric acid and calcium oxalate, especially the latter due to their high birefringence. Histologically, oxalate crystals are translucents, whereas DHA crystals are brown or yellowish-brown. Urate crystals lose their birefringence during formalin fixation and can be identified using special stains such as De Galantha and Schultz stains. The combination of polarizing microscopy and Fourier transform microscopy is a reliable method for characterizing crystals in renal biopsy.11 Measurement of the level of APRT enzymatic activity in erythrocyte lysates is a useful tool for the diagnosis of APRT deficiency but is unavailable in most countries. Molecular genetic testing, which can show functionally significant mutations in both alleles of the APRT gene, is another method to confirm diagnosis.

Treatment of APRT deficiency relies on allopurinol therapy, which acts by blocking xanthine dehydrogenase, allowing the renal function to stabilize or improve and preventing recurrence after
renal transplant. Febuxostat, another xanthine dehydrogenase inhibitor, is an alternative drug in allopurinol-intolerant patients. These medications require support with high fluid intake and dietary changes. Treatment is usually monitored by measuring crystalluria.

Screening for APRT deficiency is recommended in all cases of urinary stones in children, patients with recurrent urinary stones (especially if stones are radiolucent), and patients with history of urinary stones associated with acute or chronic kidney disease of uncertain cause (including those with end-stage renal disease and renal transplant recipients). Each sibling of a proband with APRT deficiency has a 25% chance of carrying 2 mutations and being affected. All siblings, symptomatic or not, should therefore be investigated for APRT deficiency.

Although APRT deficiency is treatable, it is often recognized late after recurrent stone episodes or once irreversible renal insufficiency has occurred. A high index of clinical suspicion and performing the appropriate investigations are mandatory for its timely management and prevention of complications, particularly regarding recurrence in the renal transplant recipient and to prevent allograft loss.

References


