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【 CASE REPORT 】

Recurrence of 2,8-dihydroxyadenine Crystalline Nephropathy in a Kidney Transplant Recipient: A Case Report and Literature Review

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Abstract:

We herein report the case of a kidney transplant patient with recurrence of obstructive nephropathy that was not diagnosed as adenine phosphoribosyltransferase (APRT) deficiency until gene testing identified a pathogenic homozygous variant three years after renal transplantation. Subsequently, the patient was treated with allopurinol, and the allograft function increased progressively to normal. In addition, 20 cases of APRT deficiency in renal transplant recipients were also reviewed. We hope this case increases awareness of APRT deficiency in repeated obstructive nephropathy post-transplantation, which is a treatable disease for which the misdiagnosis or delayed diagnosis should be avoided.

Key words: adenine phosphoribosyltransferase deficiency, 2,8-dihydroxyadenine, kidney transplantation, renal biopsy, graft loss

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Introduction

Adenine phosphoribosyltransferase (APRT) deficiency is a rare autosomal recessive metabolic disorder of adenine that is frequently overlooked by physicians, due to the absence of specific clinical manifestations and laboratory evidence (1). Recurrence of the disease in renal transplant recipients is an under-diagnosed etiology of graft dysfunction.

Cases of APRT deficiency resulting in allograft dysfunction are rarely reported. We encountered a case of recurrence of obstructive allograft nephropathy that was diagnosed as homozygous APRT deficiency by a genetic analysis three years after renal transplantation. The serum creatinine level was increased during the clinical follow-up period, and an allograft biopsy showed obstructive nephropathy caused by tubular crystal deposits. The serum creatinine level returned to normal after treatment with allopurinol. Other cases of APRT deficiency in the literature were also reviewed.

Case Report

The patient we encountered had bilateral kidney stones and left ureterolithiasis at 9 years old in 2003, and the serum creatinine was 200 μmol/L. The results of a urinalysis were not available. He had no flank pain and gross hematuria. He was diagnosed with obstructive nephropathy, and left ureterolithotomy was performed, but the stones were not sent for a chemical analysis. His serum creatinine level fluctuated between 200-300 μmol/L at regular follow-up visits and then increased gradually, eventually reaching 1,400 μmol/L in 2010. Subsequently, maintenance hemodialysis was begun and performed for six years.

In September 2016, the patient received an allograft from a 45-year-old male donor after brain and cardiac death (China type III) and all procedures followed the the Principles of the Declaration of Istanbul. Primary hyperoxaluria was ruled out (negative genetic testing of AGXT, GRHPR, and DHDPSL genes in 2015). An allograft biopsy was per-

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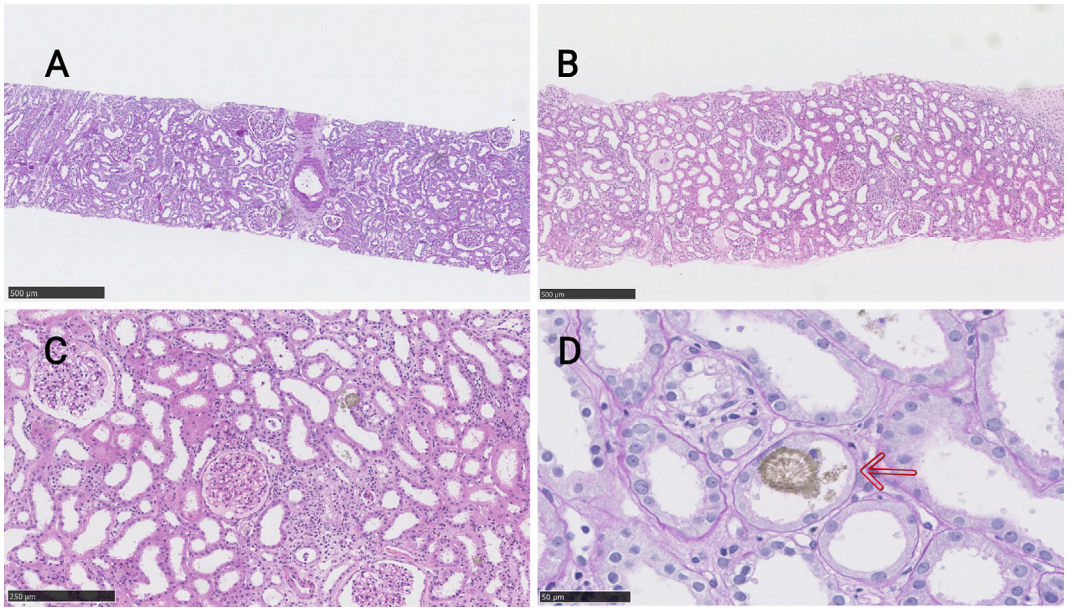

Figure 1. The first allograft biopsy after reperfusion and the second biopsy. (A) A reperfusion biopsy microphotograph showing no crystal deposition. PAS stain; scale bar A: 500 µm. (B-D) The second allograft biopsy showing tubular epithelial cell injury with crystal formation (D, red arrow). PAS stain; scale bar B: 500 µm, C: 250 µm, D: 50 µm.

formed immediately after blood reperfusion, showing normal tubular epithelial cells without crystal deposition (Fig. 1A). Immunosuppressants included basiliximab as induction and mycophenolate, tacrolimus, and steroid as maintenance. Twenty days after transplantation, the serum creatinine level remained high at 204 µmol/L, and the serum uric acid level increased to 578 µmol/L. The patient then underwent a second allograft biopsy, which revealed tubular epithelial cell injury with scattered crystalline deposition (Fig. 1B-D). Thus, the patient received allopurinol 100 mg twice a day to treat his high level of uric acid. At 6 months post-operation, the serum creatinine levels had gradually decreased to 120 µmol/L. He had no family history of marriage between cousins or renal diseases.

From January 2019, allopurinol was withdrawn, as the uric acid level had decreased to 326 µmol/L and the serum creatinine level to 132 µmol/L. Six months later, however, the allograft function deteriorated again, with a serum creatinine level of 202 µmol/L. Histopathology results revealed acute T cell-mediated rejection (type IB) based on the 2017 Banff criteria, complicated by tubular epithelial cell injury and crystallization formation in the lumen (Fig. 2). The patient received methylprednisolone intravenous injection at 500 mg/day for 3 days and successive anti-human thymocyte immunoglobin at 50 mg/day for 5 days. The patient was discharged when the serum creatinine level had decreased to 168 µmol/L. A regular follow-up laboratory examination showed that the serum creatinine level had been maintained at 180-190 µmol/L.

Two months after hospital discharge, the serum creatinine level had increased to 228 µmol/L, with the uric acid level again at 416 µmol/L. A fourth renal allograft biopsy showed no obvious T cell-mediated rejection, but tubular epithelial cell injury was noted, along with crystal formation with inflammation cells around the crystal (Fig. 3). A genetic analysis was then performed and showed one homozygous variant with deletion of phenylalanine as well as serine and an insertion of a serine into amino acids 174 and 175; NM_000485(of the APRT gene): c.521_523delTCT (p.174_175delFSinsS), defined as having pathogenic significance according to The American College of Medical Genetics and Genomics (ACMG) guideline. The patient was subsequently treated with allopurinol, 200 mg/day, and a low-purine diet as well as ensuring sufficient fluid intake. His renal function eventually improved, with a follow-up serum creatinine level of 124 µmol/L and uric acid level of 297 µmol/L in July 2020.

Literature review

Twenty cases of APRT deficiency in renal transplantation patients were identified in our search of PubMed (2-18), summarized in Table. The following keywords were used: "Adenine phosphotransferase deficiency" OR "APRT deficiency" OR "2,8-dihydroxyadenine" OR "2,8-DHA" in combination with "transplant." The search publication date was from January 1, 1974, to July 1, 2020. There were 24 grafts in total. Information on the clinical manifestation was not available for one graft and was urolithiasis in five grafts, cloud urine in one graft, a delayed graft function in nine grafts, acute graft dysfunction in three grafts, and chronic graft dysfunction in five grafts. The diagnostic methods were a stone/crystal analysis (3 cases); a stone/crystal analysis and enzyme assay (5 cases); an enzyme assay only (5 cases); a stone/crystal analysis, enzyme assay, and gene

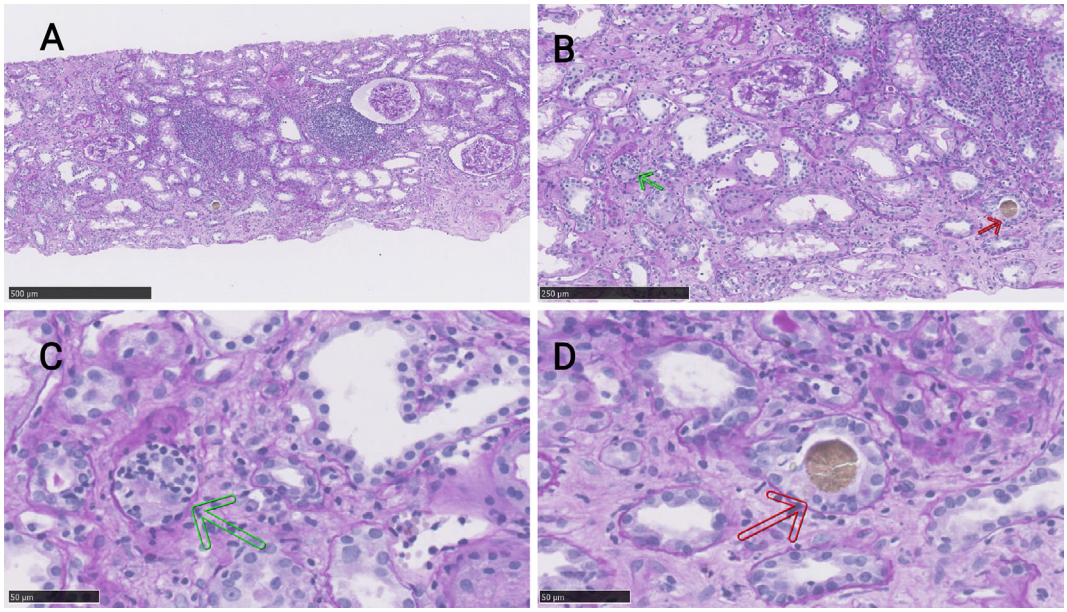

Figure 2. **The third biopsy. The third biopsy showing Type IB T cell-mediated rejection, tubulitis (B and C, green arrow), and crystal deposition in the tubular lumens (B and D, red arrow). PAS stain; scale bar A: 500 μm, B: 250 μm, C: 50 μm, D: 50 μm.**

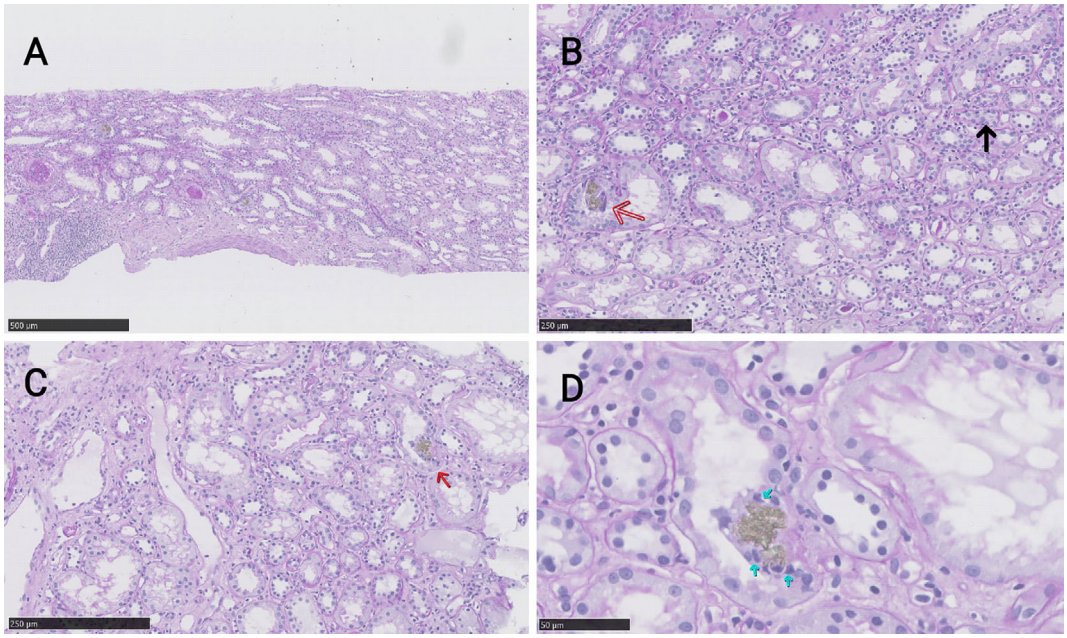

Figure 3. **The fourth biopsy. The fourth biopsy showing improvement of T cell-mediated rejection but notable crystal deposition (B and C, red arrow), tubulitis (B, black arrow), and crystals surrounded by mononuclear cell infiltrates (D, blue arrow). PAS stain; scale bar A: 500 μm, B: 250 μm, C: 50 μm, D: 50 μm.**

analysis (3 cases); a gene analysis (1 case); and a stone/crystal analysis and gene analysis (1 case). Details concerning the specific treatment were not available in one graft and were no treatment in five grafts; allopurinol, low purine, and hydration in five grafts; allopurinol and low purine in five grafts; allopurinol in five grafts; febuxostat, low purine, and hydration in one graft; and allopurinol and febuxostat in two grafts. Outcomes were unavailable in 1, graft loss in 11 (with no treatment in 5 and treatment in 6), and renal function improvement in 12.

Discussion

APRT deficiency is a rare autosomal recessive hereditary disease of purine metabolism dysfunction. Adenine is normally converted to adenine monophosphate by APRT but is

Table. Review of Reported Cases of APRT Deficiency in Kidney Transplant Recipients.

Reference	Graft number	Clinical manifestation	Specific treatment	Allopurinol/febuxostat dosage			Renal outcome
				Initiation	Maximum	maintenance	
2	1	Urolithiasis	Allopurinol low purine Hydration	4 mg/kg/d	8 mg/kg/d	2 mg/kg/d	Renal function improved
3	1	CGD	Allopurinol low-purine	100 mg/d	100 mg/d	100 mg/d	Graft loss
4	1	CGD	Not treated	-	-	-	Graft loss
5	1	CGD	Not treated	-	-	-	Graft loss
6	1	AGD	Allopurinol Low purine Hydration	10 mg/kg/d	10 mg/kg/d	10 mg/kg/d	Renal function improved
7	1	Urolithiasis	Allopurinol Low purine Hydration	100 mg/d	300md/d	300md/d	Renal function improved
8	1	Urolithiasis	Allopurinol Low-protein Hydration	NA	NA	NA	Renal function improved
9	1	DGF	Allopurinol Low-purine	300 mg/d	300 mg/d	300 mg/d	Renal function improved
10	1st	Urolithiasis	Not treated	-	-	-	Graft loss
	2nd	DGF	Allopurinol	NA	NA	NA	Graft loss
	3rd	DGF	Allopurinol Low-purine	150 mg/d	300 mg/d	300 mg/d	Graft loss
11	1st	AGD	Not treated	-	-	-	Graft loss
	2nd	CGD	Allopurinol Low-purine	200 mg/d	200 mg/d	200 mg/d	Graft loss
11	1	CGD	Allopurinol Low-purine	200 mg/d	400 mg/d	400 mg/d	Graft loss
11	1	DGF	Allopurinol	300 mg/d	600 mg/d	600 mg/d	Renal function improved
12	1	DGF	NA	NA	NA	NA	NA
13	1st	Urolithiasis	Not treated	-	-	-	Graft loss
	2nd	DGF	Allopurinol	300 mg/d	500 mg/d	500 mg/d	Graft loss
14	1	DGF	Allopurinol	200 mg/d	200 mg/d	200 mg/d	Renal function improved
15	1	NA	Allopurinol	300 mg/d	300 mg/d	300 mg/d	Renal function improved
16	1	cloudy urine	Febuxostat Low purine Hydration	20 mg/d	80 mg/d	80 mg/d	Renal function improved
17	1	AGD	Allopurinol Low purine Hydration	200 mg/d	200 mg/d	200 mg/d	Renal function improved
18	1	DGF	Allopurinol Febuxostat	100 mg/d	600 mg/d (allopurinol) 60 mg/d (febuxostat)	600 mg/d (allopurinol) 60 mg/d (febuxostat)	Renal function improved
18	1	DGF	Allopurinol Febuxostat	300 mg/d	200 mg/d (allopurinol) 40 mg/d (febuxostat)	200 mg/d (allopurinol) 40 mg/d (febuxostat)	Renal function improved

APRT: adenine phosphoribosyl transferase, CGD: chronic graft dysfunction, AGD: acute graft dysfunction, DGF: delayed graft function, NA: not available

instead oxidized by xanthine dehydrogenase through an 8-hydroxy intermediate to 2,8-DHA due to the deficiency of this salvage enzyme (6). The disease is currently underdiagnosed due to a lack of awareness about this disease among physicians as well as a lack of specific clinical manifestations, which can include crystalline nephropathy, urolithiasis, renal colic, chronic kidney disease, and allograft dysfunction (7, 19, 20).

Urolithiasis is the most common clinical manifestation of this disease and can occur at any age; in at least 50% of patients, symptoms do not occur until adulthood (19). Recurrence of 2,8-dihydroxyadenine crystalline nephropathy in renal transplantation can lead to allograft dysfunction. Twenty cases of APRT deficiency in renal transplant patients have been reviewed (Table). Urolithiasis and crystal deposition in the allograft resulted in graft dysfunction, acute in some cases and chronic in others. Cloud urine caused by 2,8-DHA crystal excretion was also a significant clinical manifesta-

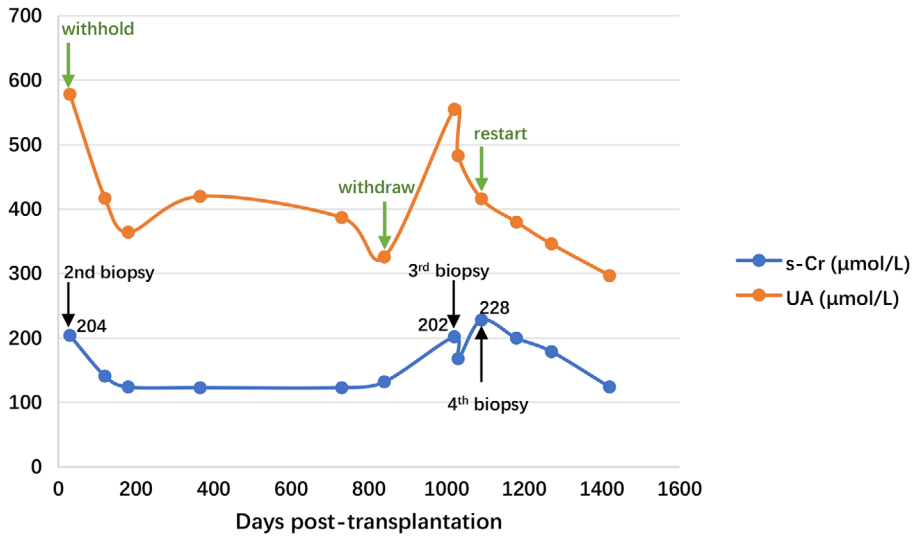

Figure 4. **The clinical course of s-Cr, UA, and allopurinol administration (withhold, withdraw and re-start) as well as the biopsies (second, third, and fourth). s-Cr: serum creatinine, UA: uric acid**

tion. One crucial manifestation of graft dysfunction-anuria or oliguria-was found in these patients (4, 5, 11, 13, 14), and their biopsies showed crystal deposition in renal tubules leading to tubular obstruction. Thus, patients who receive grafts and display anuria or oliguria should be suspected of having 2,8-DHA crystal deposition in their renal tubules.

A correct diagnosis and timely therapy can typically improve the graft function, but if a timely diagnosis cannot be made or the right therapy cannot be administered after renal transplantation, this disorder ran result in graft loss. It is more important, however, to accurately diagnose this disease prior to kidney transplantation and prevent its recurrence. APRT deficiency should be suspected in patients with unexplained renal failure or recurrent urinary lithiasis of undetermined composition, especially in those with a history of urolithiasis during childhood or crystalline nephropathy or suspected chronic tubulointerstitial nephritis of unknown etiology, or in those suspected of having autosomal recessive inheritance especially for those who have family history of marriage with a cousin or relative.

2,8-DHA is protein-bound in plasma but poorly soluble in the urine at any physiological pH and forms crystals in tubular lumens, tubular epithelial cells, and the interstitium, resulting in inflammation, necrosis, and fibrosis (15, 21-23). Notably, inflammation is characterized by mononuclear cell infiltrates (23), and 2,8-DHA crystals are surrounded by giant cells as well as macrophages on renal biopsies (4, 15, 17, 22). Inflammation and necrosis accompanied by crystal deposition may be confused with rejection in transplant patients. In the present patient, the fourth biopsy demonstrated histological injury similar to rejection, but no anti-rejection therapy was administrated. Treatment with allopurinol was performed to reduce the 2,8-DHA crystalline formation, and subsequently, the serum creatinine level decreased. This suggested that the infiltration of inflammatory cells in the allograft might have been induced by crystal deposition caused by 2,8-DHA, leading to rejection-like changes at the second biopsy. It is important to differentiate inflammatory changes caused by 2,8-DHA from rejection.

Furthermore, the recurrence of urolithiasis needs to detected as soon as possible. Identifying the characteristic 2,8-DHA crystals in urine or renal biopsy specimens is necessary for the diagnosis, as in some cases, there are no obtainable stones. In most crystalluria specimens, 2,8-DHA crystals are round and reddish-brown when viewed by urine microscopy and show a typical central Maltese cross pattern on polarized light microscopy. In the clinical field, Fourier transform infrared microscopy has been accepted as an accurate method for identifying 2,8-DHA crystals (20, 22, 24). However, a diagnosis of APRT deficiency based on the analysis of 2,8-DHA crystals and urolithiasis is not sufficient. Measurement of the APRT activity in red cell lysates or the performance of molecular genetic testing is suggested to confirm the diagnosis of this disorder. (20, 22) A stone analysis and the APRT activity in red cell lysates were not performed in our patient. Instead, genetic testing was performed, showing a pathogenic homozygous variant.

The correct therapy should be given to patients diagnosed with APRT deficiency. Low doses of allopurinol and/or febuxostat did not effectively inhibit the formation of 2,8-DHA crystals (2, 7, 11, 13, 16, 18). High doses of allopurinol (up to 600 mg, even 10 mg/kg/day) and/or febuxostat (80 mg) have been required to achieve effective inhibition of 2,8-DHA crystal formation (2, 6, 16, 18). Doses of allopurinol and febuxostat are mostly empiric due to a lack of available laboratory measurements of 2,8-DHA to direct therapy. Based on the limited data shown in Table and the recommendation of Nasr et al. (11), high doses of allopurinol (≥400 mg/day) and/or febuxostat (≥40 mg/day) may be useful for treating 2,8-DHA crystalline nephropathy. Notably, side effects, such as eosinophilia, rash, liver dysfunction, and gastrointestinal reaction, should be considered when ad-

ministering high doses of allopurinol and/or febuxostat (18).

Importantly, kidney transplant recipients treated with allopurinol should not be recommended to take azathioprine and mercaptopurine (19). Urinary alkalization is useless because 2,8-DHA remains insoluble at the physiological urine pH. Of note, the prescribed dose of these drugs should not be routinely reduced in patients with renal dysfunction (19). In addition, treatment with xanthine dehydrogenase should be continued throughout the patient's life, as this disorder involves a lifelong inborn deficiency of APRT. In our case (Fig. 4), after the second renal biopsy, the patient had high uric acid levels and was treated with allopurinol to reduce these elevated levels. The renal function was stable in the following years, with the uric acid level remaining normal. Long-term maintenance with allopurinol in our patient actually inhibited the formation of 2,8-DHA. However, after the patient stopped taking allopurinol, the serum creatinine level increased, with evidence of crystal formation found in the tubule and acute rejection noted at the third and fourth renal allograft biopsies. In particular, when the patient had experienced obvious acute rejection at the third biopsy and received effective anti-rejection treatment with serum creatinine decreasing in a short time, a biopsy (fourth biopsy) performed two months later showed no obvious rejection, aside from crystal deposition in the lumen, and the patient benefited from the treatment of allopurinol despite no anti-rejection therapy being administered. This underscored the importance of lifelong treatment with allopurinol.

In summary, APRT deficiency is underdiagnosed as the etiology of allograft dysfunction due to a lack of awareness of this disease. This case and literature review described the recurrence of 2,8-DHA crystalline nephropathy in kidney transplants. A stone analysis and genetic testing should be urgently performed for the diagnosis. Sufficient awareness should be available for this treatable disorder, as severe renal complications can be prevented by a timely, correct diagnosis as well as the prompt administration of therapy.

Written informed consent for publication of the clinical details and clinical images was obtained from the patient and is available for review on request.

The authors state that they have no Conflict of Interest (COI).

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