



Renal hypouricemia in a recipient of living-donor kidney transplantation: a case report and literature review

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Received: 24 June 2021 / Accepted: 15 September 2021 / Published online: 23 September 2021
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Abstract

Hypouricemia in kidney transplant (KT) recipients is rare since they usually have subnormal kidney function which raises serum uric acid level. Recently, interests in pathogenesis of hypouricemia have been increasing due to the understanding of the role of uric acid transporter in renal hypouricemia (RHUC). We herein report the case of RHUC consequently developed in a KT recipient from a living donor with RHUC diagnosed by the detailed urinary and genetic test. A 73-year-old Japanese man underwent KT, and the donor was his wife who had hypouricemia [serum uric acid (S-UA) 0.6 mg/dL]. Nine months after KT, the recipient's S-UA was low (1.5 mg/dL) with serum creatinine (S-Cr) of 1.56 mg/dL, and fractional excretion of UA (FEUA) was high (59.7%; normal < 10%), indicating RHUC. Regarding the donor's information, S-Cr, S-UA, and FEUA were 0.95 mg/dL, 1.0 mg/dL, and 54.5%, respectively. To investigate further on the pathogenesis of RHUC in both the recipient and the donor, we performed genetic tests. The donor had a homozygous mutation of W258X in the *SLC22A12* gene and the recipient had a wild type of W258X. Finally, we reviewed the previous literature on RHUC among KT recipients and discussed the strategy of follow-up for these patients.

Keywords Hypouricemia · Renal hypouricemia · Kidney transplantation · Living donor

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Introduction

In daily clinical practice, hyperuricemia gained more focus than hypouricemia, since the former is more common and is related not only to gout and nephrolithiasis but also to cardiovascular disease [1]. On the other hand, hypouricemia is overlooked owing to its rarity and the usual presentation of no symptoms. Recently, hypouricemia has gained more interests due to recent progress in understanding of the role of uric acid transporters, and its recognition of renal hypouricemia (RHUC) as a disease, which often complicates kidney stones and exercise-induced acute kidney injury (EIAKI) [2]. The diagnosis of RHUC is based on hypouricemia (serum uric acid (UA) < 2.0 mg/dL) and an increase in both fractional excretion of uric acid (FEUA) and clearance of UA (CUA), without other secondary causes of hypouricemia. RHUC type 1 is caused by a mutation in the *SLC22A12* gene which encodes a renal urate-anion exchanger, named URAT1 (urate transporter 1), along the apical membrane of the proximal tubule. While RHUC type 2 is caused by a defect in the *SLC2A9* gene that encodes a high-capacity urate transporter, named GLUT9 (glucose transporter like protein 9), along the basolateral membrane of the proximal tubule. The prevalence of RHUC is less than 0.5% in general population [3, 4], and its prevalence among women is higher than that among men in Japan [4]. Hypouricemia, especially RHUC, is often accompanied with kidney stones and EIAKI [5], with an incidence of 8.5% and of 6.5%, respectively [6].

Kidney transplantation (KT) from donors with RHUC could possibly put recipients on the risk of hypouricemia since they excrete urine from affected donor kidney with aforementioned mutations. RHUC in KT recipients may cause kidney stones or EIAKI after KT. A few case reports have documented RHUC in either recipients or living donors following KT. However, comprehensive clinical data are scarce regarding KT recipients and donors in the literature.

We herein report a case of RHUC that developed in a recipient from a living donor with hypouricemia. We also underwent a literature review of RHUC in KT recipients and discussed an ideal follow-up strategy for these patients.

Case

A 73-year-old Japanese man with a 2 year history of maintenance hemodialysis underwent living-donor and ABO-compatible KT 1 year ago in our transplant center. The numbers of human leukocyte antigen (HLA) mismatches

was 4. The etiology of his renal failure was suspected to be IgA nephritis without kidney biopsy. No past history of hypouricemia, kidney stones, and EIAKI were documented. His family history also was not remarkable for hypouricemia. His laboratory results before KT showed a serum UA (S-UA) level of 8.1 mg/dL even with febuxostat (Table 1).

The living donor was his 71-year-old wife. Before KT, her serum creatinine (S-Cr) was 0.64 mg/dL, S-UA was 0.6 mg/dL, and FEUA was 24.9% which was consistent with RHUC (Table 2) but without genetic testing. The donor and her family had no history of hypouricemia or related diseases such as kidney stones and EIAKI (Fig. 1). As there was no consensus in terms of UA threshold of each low and high level for living kidney donation, we did not perform a genetic test for the definitive diagnosis of hypouricemia prior to donation, and accepted her as an eligible living donor.

Table 1 Laboratory data before and after kidney transplantation of the recipient

	Pre-kidney transplantation	9 months after kidney transplantation
Complete blood cell count and serum chemistries		
White blood cell ($\times 10^9/L$)	5.3	5.4
Hemoglobin (g/dL)	10.0	13.7
Hematocrit (%)	29.2	43.1
Platelets ($\times 10^9/L$)	29.2	10.4
Total protein (g/L)	6.4	6.8
Albumin (g/L)	3.7	4.2
Blood urea nitrogen (mg/dL)	33.0	25.6
Creatinine (mg/dL)	On dialysis	1.56
Uric acid (mg/dL)	8.1	1.5
Sodium (mEq/L)	138	140
Potassium (mEq/L)	5.1	4.1
Chloride (mEq/L)	112	107
Calcium (mg/dL)	8.9	9.2
Phosphate (mg/dL)	3.4	3.0
Urinalysis		
pH	5.5	6.0
Urinary protein	(2+)	(-)
Occult blood	(±)	(-)
RBC sediment (per HPF)	1–4	< 1
WBC sediment (per HPF)	1–4	< 1
CCr (mL/min/1.73 m ²)	On dialysis	49.3
Urine UA (mg/day)	N/A	629.3
UA clearance (mL/min)	N/A	29
FEUA (%)	N/A	59.7

HPF high power field, RBC red blood cell, WBC white blood cell, CCr creatinine clearance, UA uric acid, FEUA fractional excretion of uric acid, N/A not available

Table 2 Laboratory data before and after kidney transplantation of the donor

	Pre-kidney transplantation	Nine month after-kidney transplantation
Complete blood cell count and serum chemistries		
White blood cell ($\times 10^9/L$)	7.8	7.2
Hemoglobin (g/dL)	13.3	13.3
Hematocrit (%)	39.6	40.6
Platelets ($\times 10^9/L$)	22.4	21.8
Total protein (g/L)	7.5	7.6
Albumin (g/L)	4.6	4.4
Blood urea nitrogen (mg/dL)	13.1	16.0
Creatinine (mg/dL)	0.64	0.95
Uric acid (mg/dL)	0.6	1.0
Sodium (mEq/L)	141	140
Potassium (mEq/L)	3.9	4.4
Chloride (mEq/L)	105	104
Calcium (mg/dL)	9.6	9.3
Phosphate (mg/dL)	4.2	4.0
Urinalysis		
pH	6.5	6.0
Urinary protein	(–)	(–)
Occult blood	(–)	(–)
RBC sediment (per HPF)	<1	<1
WBC sediment (per HPF)	<1	<1
CCr (mL/min/1.73 m ²)	111.8	77.1
Urine UA (mg/day)	539.0	488.6
UA clearance (mL/min)	27.9	42.0
FEUA (%)	24.9	54.9

HPF high power field, RBC red blood cell, WBC white blood cell, CCr creatinine clearance, UA uric acid, FEUA fractional excretion of uric acid, N/A not available

The clinical course of KT regarding both donor and recipient was stable. Conventional maintenance immunosuppressive therapy comprising steroids, extended-release tacrolimus, and mycophenolate mofetil was administered. Two weeks after KT, the recipient's S-Cr was 1.72 mg/dL and his S-UA was 1.5 mg/dL without any medication for hyperuricemia. Nine months after KT, the recipient's S-Cr was stable (1.56 mg/dL), while level of S-UA remained low (1.5 mg/dL), with high FEUA (59.7%; normal < 10%), and high CUA (29 mL/min) (Table 1). In terms of donor's UA status after donation, S-UA was 1.0 mg/dL when s-Cr was 0.95 mg/dL, with high FEUA (54.5%) and high CUA (42 mL/min) (Table 2). Table 3 also shows the changes in the FEUA, S-UA, and S-Cr levels, and glomerular filtration rate (GFR) in both the recipient and the donor.

Hypouricemia developed in the recipient was apparently due to implanted donor kidney, which strongly indicates the diagnosis of RHUC, we decided to perform a genetic test

after obtaining informed consent. The donor had a homozygous mutation of W258X in the *SLC22A12* gene and the recipient had a wild type W258X. Based on these genetic results, hypouricemia in the donor resulted in RHUC type 1 and the recipient was consequently affected owing to the donated kidney.

The donor's and recipient's S-UA and S-Cr levels did not significantly change during the first year following KT. The protocol (non-indication) allograft biopsies of the recipient were done at the bench (0 h), 2 months, and 1 year after KT. There was no evidence of rejection, recurrence of IgA nephritis, any casts, any crystals/calcified lesions or nephrolithiasis. Furthermore, both the recipient and donor did not have any stones in the urinary tract by the CT scanning. Based on the definitive diagnosis, we have strived to prevent RHUC-related complications in both the donor and recipient during post-KT follow-ups. In particular, we have advised avoiding extreme anaerobic exercise with non-steroidal anti-inflammatory drugs (NSAIDs) to prevent EIAKI and drinking water (1.5–2 L/day), and we ensured to check their urinary pH (ideally pH > 6.5) during every checkup to prevent the formation of urinary stones.

Discussion and the literature review

We reported a case of KT from a donor with a homozygous mutation of W258X in the *SLC22A12* gene diagnosed as RHUC type 1. Although we noticed extremely low levels of UA before donation which suspected RHUC without the genetic test, there has been no consensus in terms of UA threshold of each low and high level for living kidney donation [7, 8]. We indicated any harms of RHUC to both the donor and recipient after donor nephrectomy and deeply discussed that with transplant team. The donor and recipient consented to undergo KT; and thus, we decided the eligibility for donation. After KT, the recipient had relatively low levels of UA even with mild kidney dysfunction. We suspected the cause and transmission of hypouricemia to be the donated kidney and suspected a diagnosis of RHUC. We performed a genetic test for both the donor and recipient to obtain the accurate diagnosis and assess the risk of urinary stones formation and EIAKI development, since both the donor and recipient had a single kidney. Furthermore, the genetic type of RHUC is important for risk assessments. RHUC type 1, a mutation in the *SLC22A12* gene, is more frequent than RHUC type 2 [6, 9, 10] W258X is the most prevalent mutation in RHUC type 1 and it has been reported in several reports (74.1% [11] and 79.7% [11]). Particularly, homozygous W258X mutation is the most frequent mutation in Japan (54.8%) and in Korea (42%) [11]. RHUC patients having at least one W258X mutation tended to experience urinary stones, AKI, or hematuria [11]. However, these

Fig. 1 Family tree of both the recipient and donor. * represents no information regarding mutation of RHUC. Circles represent female gender and squares represent male gender. Whole Black circle represents homozygous mutation of W258X in the *SLC22A12* gene. Half black circle and square represent heterozygous mutation of W258X in the *SLC22A12* gene. Crosses represent dead family members

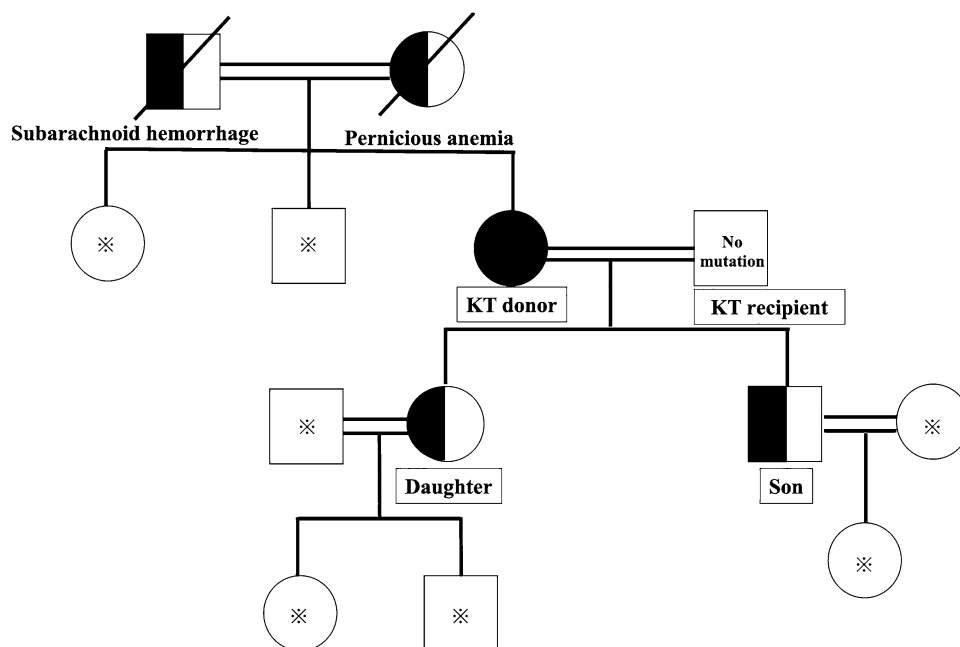


Table 3 Laboratory data regarding kidney function and uric acid-related parameters of the recipient and donor at 2 weeks, 3 months, 9 months, and 1 year post-kidney transplantation

	2 weeks	3 months	9 months	1 year
Recipient				
CCr (mL/min/1.73 m ³)	N/A	N/A	49.3	N/A
UA clearance (mL/min)	N/A	N/A	29	N/A
FEUA (%)	N/A	N/A	59.4	60.4
Serum UA (mg/dL)	1.5	1.6	1.5	1.8
Serum Cr (mg/dL)	1.72	1.68	1.56	1.79
eGFR(mL/min/1.73 m ²)	31.4	32.2	34.8	30.0
Donor				
CCr (mL/min/1.73 m ³)	N/A	N/A	77.1	N/A
UA clearance (mL/min)	N/A	N/A	42	N/A
FEUA (%)	N/A	N/A	54.9	50.3
Serum UA (mg/dL)	1.2	1.0	1.0	1.1
Serum Cr (mg/dL)	1.02	1.0	0.95	0.93
eGFR (mL/min/1.73 m ²)	41.4	42.4	44.6	45.7

CCr creatinine clearance, UA uric acid, FEUA fractional excretion of uric acid, eGFR estimated glomerular filtration rate, N/A not available

reports were on the general population and not from kidney transplant patients. Interestingly, the donor's FEUA after donation was increased compared to that prior to donation, which represents reduction in her GFR, in accordance with the principle of fractional excretion (Table 2). FEUA is the ratio of urinary UA concentration and urine volume to the product of serum UA concentration and GFR. Thus, the decreased GFR reflects the increased FEUA.

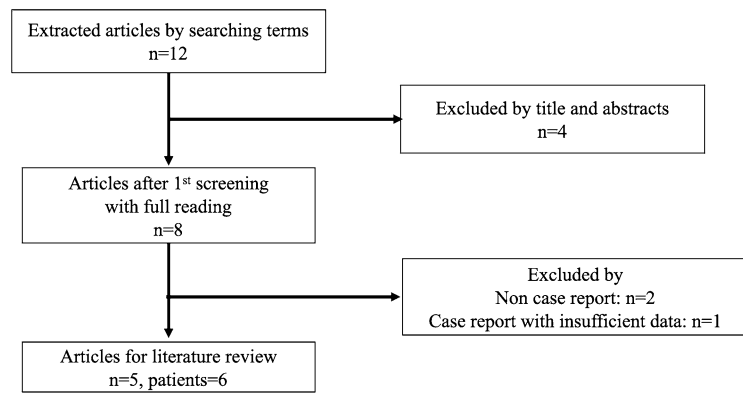
Moreover, we indirectly proved the transmission of RHUC via the donated kidney with a mutation of W258X

in the *SLC22A12* gene, since the recipient's FEUA and GFR, which reflects fractional excretion, was almost the same with the donor's FEUA, despite of no mutation of W258X in the *SLC22A12* gene in recipient (Table 1).

Since there are scarce clinical data on RHUC in KT, we performed a literature review based on past case reports on MEDLINE (PubMed). Literature review was separately done by two authors (T. M. and M. Y.) according to the searching terms describing on Fig. 2. We eventually found 5 reports and 6 cases, this data is summarized in Tables 4 and 5. Cases of living KT donors occupied the majority (4 out of 6 cases). All genetic abnormalities were in the *SLC22A12* gene and only one of these patients experienced urinary stone. The differences between our case as compared to the previous reports are as follows: we have (1) detailed urinary data (FEUA and UA clearance) of both the donor and recipient and (2) detailed genetic information (mutation of W258X in *SLC22A12* gene). Only our case demonstrated high FEUA and UA clearance in both the recipient and donor consisting of RHUC. According to the review of the literature, the incidence of urinary stone and EIAKI in either the KT recipient or donor with RHUC were not concluded due to a small number of patients in previous studies.

Finally, although we do not have data on whether the recipient and donor of KT with RHUC have high incidence of kidney stones or EIAKI, we should focus on preventing these complications based on the evidence obtained from the general population, since the recipient and donor both have a single kidney and a mutation of W258X, which is highly likely to cause those complications. In this regard, it is best to avoid extremely hard and anaerobic exercise, to be adequately hydrated [12], and to have urine alkalisers

Fig. 2 Flowchart diagram of the literature searching among kidney transplant recipients with renal hypouricemia



The searching terms on Pubmed: ((kidney Transplantation [tiab] OR Renal Transplantation [tiab] OR Renal Transplantations [tiab] OR Transplantations, Renal [tiab] OR Transplantation, Renal [tiab] OR Grafting, Kidney [tiab] OR Kidney Grafting [tiab] OR Transplantation, Kidney [tiab] OR Kidney Transplantations [tiab] OR Transplantations, Kidney[tiab] OR kidney transplant recipient [tiab] OR kidney transplant recipients[tiab]) AND (hypouricemia [tiab] OR low uric acid [tiab] OR decreased uric acid [tiab] OR renal hypouricemia [tiab] OR hypouricemia, renal [tiab] OR urate transporter [tiab] OR urate transporter 1 [tiab] OR urate transporter 1 protein, human [mh] OR URAT [tiab] OR URAT1 protein, human [mh] OR URAT 1 [tiab] OR SLC22A12 protein, human [mh] OR SLC22A12 [tiab]))

Table 4 Literature review of renal hypouricemia among kidney transplant recipients and our case (references [14–18])

References	Country	Type of donor	Recipient age and gender	S-UA (mg/dL) Post-KT	FEUA (%) Post-KT	UA clearance (mL/min) Post-KT	Urinary stone Post-KT	Impaired kidney function (including EIAKI)
Yamamoto et al. [14]	Japan	Living	24 Male	1.0	57.9	39.9	No	No
Juraschek et al. [15]	USA	Living	71 Female	2.7	N/A	N/A	No	No
Okabayashi et al. [16]	Japan	Living	41 Male	1.9	29	26.8	Yes	No
Teng et al. [17]	China	Deceased	41 Male	0.92–1.1	44	35.9	No	No
			37 Female	0.76–0.92	75	73.3	No	No
Tsuji et al. [18]	Japan	Living	40 Male	3.9	11.7	N/A	No	No
Our case	Japan	Living	73 Male	1.5	59.7	29	No	No

S-UA serum uric acid, FEUA fractional excretion of uric acid, KT kidney transplantation, EIAKI exercise-induced acute kidney injury, N/A not available

[13]. Our donor and recipient are above the age of 70 years and only had the habit of aerobic walking thrice a week; thus, they were less likely to perform hard or anaerobic exercise. We therefore especially focused on preventing urinary stones by keeping a check on urinary pH and maintaining it between 6.5 and 7.0 in accordance with

the recommendation to maintain the uric acid solubility [13]. The recipient and donor did not reach target range of urinary pH even though we recommend enough consumption of vegetables and fruits (Tables 1 and 2). We would recommend the use of potassium citrate or sodium bicarbonate in the near future.

Table 5 Literature review of renal hypouricemia among kidney transplant recipients and our case with donors' characteristics (references [14–18])

References	Donor's genetic abnormality	Age and gender	S-UA (mg/dL) Pre-KT	S-UA (mg/dL) Post-KT	FEUA (%) Pre-KT	FEUA (%) Post-KT	UA clearance (mL/min) Pre-KT	UA clearance (mL/min) Post-KT	Urinary stone Post-KT	Donor impaired kidney function (including EIAKI)
Yamamoto et al. [14]	<i>SLC22A12</i> (W258X homozygote)	Father Male	N/A	1.0	N/A	N/A	N/A	N/A	No	No
Juraschek et al. [15]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No	No
Okabayashi et al. [16]	N/A	Father Male	N/A	2.4	N/A	10.3	N/A	N/A	No	No
Teng et al. [17]	<i>SLC22A12</i> (R89H, L181V compound heterozygote)	30 Male	0.8	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tsuji et al. [18]	<i>SLC22A12</i> (R90H heterozygote)	42 Female	1.7	N/A	15.8	20.0	N/A	41.0	No	No
Our case	<i>SLC22A12</i> (W258X homozygote)	71 Female	0.6	1.0	24.9	54.5	87.3	42.0	No	No

S-UA serum uric acid, FEUA fractional excretion of uric acid, KT kidney transplantation, EIAKI exercise-induced acute kidney injury, N/A not available

Acknowledgements This case report has not been published previously in whole or part and supported by an grant.

Data availability All clinical data are available on the electronic medical record at St. Marianna University Hospital. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest Authors have no conflicts of interest to declare.

Informed consent We obtained informed consent from both the recipient and donor and they accepted the presentation of their clinical course, including genetic testing. The consent details are stated in the electron medical record at St. Mariann University Hospital.

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