The lowest uric acid in kidney transplant and review of literature

J. Roozbeh[1], A. Dehghani[1], A. Haghpanah[1,2], L. Malekmakan[1]*

[1]Shiraz Nephro-Urology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Endourology Ward, Urology Department, Shiraz University of Medical Sciences, Shiraz, Iran

ABSTRACT

Heredity hypouricemia is caused by renal hypouricemia or xanthinuria. Xanthinuria is divided into type 1 with deficiency of xanthine dehydrogenase and type 2 with xanthine dehydrogenase and aldehyde oxidase deficiency. We report a case of xanthinuria type 1 that developed with kidney failure. Hemodialysis was done for him, but kidney function was not improved, so a kidney transplant was performed for him. His serum uric acid was 0.1 mg/dl before and after transplantation.

KEYWORDS: Hypouricemia; Kidney transplantations; Uric acid; Xanthinuria type 1

INTRODUCTION

Hypouricemia is defined when plasma uric acid is lower than 2 mg/dl. Some medical diseases that can cause hypouricemia are Fanconi syndrome, hyperthyroidism, nephritis, Hartnup syndrome, Wilson's disease, and myeloma [1]. A study showed that the frequency of hypouricemia in male admitted patients was about 6.5% and in female admitted patients it was about 4.8% [2].

Genetic mutations in heredity hypouricemia are divided into two groups. First, relates to a mutation which causes abnormal renal function and increases uric acid excretion, which is named familial renal hypouricemia. The primary genetic mutation of familial renal hypouricemia is mutations in the gene SLC22A12, coding for human urate transporter 1 (URAT1) [3]. The other type of heredity hypouricemia mutations may cause xanthinuria. Classic xanthinuria has two categories based on enzyme deficiency; in type 1, there is reduced xanthine dehydrogenase enzyme production, and in type 2 there is deficiency in both xanthine dehydrogenase and aldehyde oxidase [3-5]. There is not much information regarding xanthinuria as it is rarely reported, but the overall incidence of type 1 and 2 xanthinuria is estimated to be 1 in every 69000 births [6]. Herein, we report a case of xanthinuria with a serum uric acid of 0.1 mg/dl who developed renal failure and underwent renal transplantation.

*Correspondence: Leila Malekmakan, MD, MPH
Assistant professor of the Department of Community Medicine, Shiraz Nephro-Urology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran,
7193635899- Khalili Street, Mollasdra Avenue, Shiraz, Iran
ORCID: 0000-0002-3868-9523
Tel: +98-711-212-7300
E-mail: malekmakan_l@yahoo.com

CASE PRESENTATION

A 41-year-old man initially presented with acute flank pain in 2009, with a serum creatinine of 6mg/dl and a uric acid of 0.1 mg/dl. Ultrasound showed bilateral small size kidneys (7-7.5 Cm) and increased cortical echogenicity without stone. Chronic kidney disease (CKD) was diagnosed, and hemodialysis was started for him twice a week. Also, he became a candidate for renal transplantation. Finally, in 2013, deceased-donor-renal transplantation

Table 1: The review of literature on hypouricemia.

Article	Place/time	Subject	Kidney	Genetic Mutation	Family History	Outcome
Siblings with Hereditary Renal Hypouricemia and EIARF [7]	Japan/2003	N=2 Age=45 & 42 Male	Pt1 / Pt2 Cr 5.1 / 2.1 UA 3.9 / 1 FEUA 46 / 65 AKI + / + Stone - / +	*SLC22A12*	Negative	**Pt1**: conservative treatment **Pt2**: ESWL
Xanthinuria type I with a novel mutation in xanthine dehydrogenase [3]	Japan/2016	N=1 Age=46 Female	UA 0.0 Stone - Cr 0.54 UX 0.39	Two mutations in *XDH* gene	Negative	Observation
Familial Renal Hypouricemia confirmed by genotyping of *SLC22A12*, and a literature review [8]	Korea/2015	N=1 Age=24 Male	Cr 1.6 UA 0.5 FEUA 23.95% AKI + Stone -	*SLC22A12*	Positive for his mother (carrier of renal hypouricemia)	Management of AKI
Transplantation of a kidney with a heterozygous mutation in the *SLC22A12* gene causing renal hypouricemia [9]	Japan/2020	N=1 Age=40 Male	Cr 12.5 UA 8.4 AKI + Stone - FEUA 20.8	*SLC22A12*	Donor (his sister) was affected by RHUC due to a heterozygous mutation in the *SLC22A12* (URAT1) gene	Developed RHUC heterozygous mutation in the *SLC22A12* (URAT1) gene
Renal hypouricemia and ARF accompanied by hyperbilirubinemia after anaerobic exercise [10]	Japan/2019	N=1 Age=37 Male	Cr 4.2 UA 2.7 FEUA 50.5 AKI + Stone -	A new genetic mutation causing RHUC was considered	Patient's older sister was reported to have hypouricemia, but the UA level was unknown	Observation
Mutational analysis of the *XDH* in a Turkish family with autosomal recessive classical xanthinuria [4]	Turkey/2003	N=2 Age=3.5 & 16 Male	Pt1 / Pt2 UA 0.0 / 0.0 Cr 0.2 / 0.6 Stone + / +	*XDH*	Mother and father were heterozygous for *XDH*	Stone passing and observation
Hypouricemia due to isolated renal tubular defect [11]	USA/1972	N=1 Age=23 Male	UA 1.3 FEUA 29.4 AKI + Stone +	Abnormality genetically renal affecting tubular uric acid reabsorption	His sister was hypouricemic	Stone passing and observation
Idiopathic renal hypouricemia: A case report and literature review [12]	China/2019	N=1 Age=35 Male	Cr 11.8 UA 4.4 AKI + Stone -	*SLC2A9* homozygous mutation was identified	Two family members of the patient had uremia	Discharge

ESWL: extracorporeal shockwave lithotripsy, EIARF: exercise-induced acute renal failure, AKI: acute kidney injury, ARF: acute renal failure, RHUC: renal hypouricemia, XDH: xanthine dehydrogenase, URAT1: Urate transporter 1, Cr: creatinine, UA: Uric acid, UX: urine xanthine, FEUA: fractional excretion of uric acid, Pt1: Patient 1

was performed for him successfully. His lab data showed a serum uric acid of 0.1 mg/dl, urine uric acid of 0.6 mg/dl, uric acid 24 hrs 26 mg/day, and a FEUA (fractional excretion of urea) of 0.58%. He did not have any medical problems in the routine follow-up until 2019, when he refused to take prescribed transplantation medications. Then, he developed severe nausea and vomiting, and in works-ups transplant rejection was suspected, and a renal biopsy was done. After successful management, the transplantation drugs were restarted for him. The unique manifestation of this patient is his constant serum uric acid of 0.1 mg/dl during the whole course of his disease from the first presentation till now. All his immediate family members were evaluated for hypouricemia or kidney stones, which were normal.

DISCUSSION

Xanthinuria causes xanthine accumulation in the serum and urine or tissue, leading to urinary tract stones, renal failure, or myositis [5]. Herein, we report a case of a possible xanthinuria type 1 with a serum uric acid of 0.1 mg/dl that developed with renal failure for whom renal transplantation was done.

As mentioned in Table 1, urinary tract stones are one of the symptoms of xanthinuria due to the deposition of xanthine in the urinary tract. Gok et al. reported a Turkish family in whom 2 brothers were diagnosed with xanthinuri and both developed with renal xanthine stones [4]. Contrary to this article, our patient did not have kidney stones.

In xanthinuria, while some patients are asymptomatic, others suffer from kidney failure and, in the long term, may present with small size kidney and increased serum creatinine [5]. Renal failure can be eliminated by hemodialysis and pharmacotherapy. Still, in our case, unresolved kidney problems in the long term, caused chronic kidney failure and was not controlled by routine hemodialysis, so the patient underwent a kidney transplant.

Hypouricemia is defined by serum uric acid lower than 2 mg/dl. As we mentioned, xanthinuria is an asymptomatic disease; most patients accidentally notice the condition by checking serum uric acid levels. Iguchi et al. reported a 46-year-old case with an asthma attack. Her lab data incidentally showed a serum uric acid of 0 mg/dl, and further workups showed an average kidney size and normal function with no stones. Also, she was diagnosed with xanthinuria by genetic study [3]. In our case, serum uric acid was 0.1 mg/dl before and after kidney transplantation. However, we could not perform a gene study in our case because the patient did not consent to do so. The difference between our case and those in recent studies is that our patient did not have typical symptoms like kidney stones. Still, the patient developed CKD due to negligence of symptoms; these eventually led the patient to kidney transplantation.

In conclusion, we reported a case of kidney failure with serum uric acid of 0.1 mg/dl in whom a kidney transplant was done. Despite the lack of access to the patient's genetic study and considering that no typical symptoms such as kidney stones existed, due to the constant uric acid before and after transplantation, our patient is suspected of having xanthinuria type 1.

FINANCIAL SUPPORT:

The vice-Chancellery of Research and Technology of Shiraz University of Medical Sciences financially supported this study (Grant No. 23858).

ACKNOWLEDGMENTS

The authors would like to thank Shiraz University of Medical Sciences and also Center for Development of Clinical Research of Nemazee Hospital and Dr. Nasrin Shokrpour for editorial assistance.

CONFLICTS OF INTEREST: None declared.

REFERENCES

1. Toncev G, Milicic B, Toncev S, Samardzic G. Serum uric acid levels in multiple sclerosis patients correlate with activity of disease and blood–brain barrier dysfunction. *Eur J Neurol* 2002;**9**:221-6.
2. Crook M. Hypouricaemia in a hospital population. *Scand J Clin Lab Invest* 1993;**53**:883-5.
3. Iguchi A, Sato T, Yamazaki M, *et al*. A case of xanthinuria type I with a novel mutation in xanthine dehydrogenase. *CEN Case Rep* 2016;**5**:158-62.
4. Gok F, Ichida K, Topaloglu R. Mutational analysis of the xanthine dehydrogenase gene in a Turkish family with autosomal recessive classical xanthinuria. *Nephrol Dial Transplant* 2003;**18**:2278-83.
5. Ichida K, Amaya Y, Kamatani N, *et al*. Identification of two mutations in human xanthine dehydrogenase gene responsible for classical type I xanthinuria. *J Clin Invest* 1997;**99**:2391-7.
6. Harkness R, McCreanor G, Simpson D, MacFadyen I. Pregnancy in and incidence of xanthine oxidase deficiency. *J Inherit Metab Dis* 1986;**9**:407-8.
7. Tanaka M, Itoh K, Matsushita K, *et al*. Two male siblings with hereditary renal hypouricemia and exercise-induced ARF. *Am J Kidney Dis* 2003;**42**:1287-92.
8. Kim HO, Ihm C-G, Jeong KH, *et al*. A case report of familial renal hypouricemia confirmed by genotyping of SLC22A12, and a literature review. *Electrolyte Blood Press* 2015;**13**:52-7.
9. Tsuji K, Kitamura M, Muta K, *et al*. Transplantation of a kidney with a heterozygous mutation in the SLC22A12 (URAT1) gene causing renal hypouricemia: a case report. *BMC Nephrol* 2020;**21**:1-6.
10. Furuto Y, Kawamura M, Namikawa A, *et al*. Nonurate transporter 1, non-glucose transporter member 9-related renal hypouricemia and acute renal failure accompanied by hyperbilirubinemia after anaerobic exercise: a case report. *BMC Nephrol* 2019;**20**:433.
11. Greene ML, Marcus R, Aurbach G, *et al*. Hypouricemia due to isolated renal tubular defect: Dalmatian dog mutation in man. *Am J Kidney Dis* 1972;**53**:361-7.
12. Wang C, Wang J, Liu S, *et al*. Idiopathic renal hypouricemia: A case report and literature review. *Mol Med Rep* 2019;**20**:5118-24.