

Early onset gout and chronic kidney disease in a young female patient

Yu Cao, Xin-Xin Han, Xiao-Xue Wang, Yun Zhang, Xue-Jun Zeng

Department of General Internal Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100730, China.

To the Editor: In 2018, a 31-year-old woman presented at our hospital with a 10-year history of chronic arthritis and chronic kidney disease (CKD). Arthritis occurred after a traumatic injury of her left ankle. She was then prescribed analgesics, and the symptoms were quickly resolved. Her serum uric acid (sUA) and serum creatinine (SCr) were both slightly elevated. Later on, the patient suffered joint pain on several occasions; the pain was triggered by a strain of the ankle or consumption of seafood and was most prominent at night. During each painful episode, the symptoms rapidly developed within 24 h, accompanied by skin redness and joint swelling, and decreased within a week. In the years that followed, she experienced similar attacks in her right ankle, wrists, and multiple small joints of her hands and feet, without preceding trauma. The patient was then diagnosed with gout and CKD at a local clinic. She intermittently took benzbromarone and anti-inflammatory medication for gout (benzbromarone was discontinued 8 years ago), and Shen shuai ning (a Chinese patent medication) for CKD.

SUA and SCr were not closely monitored during the treatment. The condition quickly progressed. Six years ago, numerous tophi occurred on her right auricular surface, knees, first metatarsophalangeal joints, and other joints of her hands and feet. Three years before admission, the patient developed microcytic anemia (hemoglobin [HGB] 78 g/L), while sUA and SCr were 723 and 184 $\mu\text{mol/L}$ (estimated glomerular filtration rate [eGFR] 36.53 mL/min per 1.73 m^2), respectively. The frequency (from once every 2 months to once a month) and intensity of pain increased. The duration of each episode was also prolonged. Three months before admission, she suffered severe disabling pain in the left ankle, accompanied by intermittent pain and swelling of a number of other joints. The patient took allopurinol for approximately one month. She then consulted the clinic and was encouraged to consume more water. She was also prescribed

intramuscular compound betamethasone injection for temporary symptom relief.

Later, the patient was admitted to our hospital for further investigation. She denied edema and reported normal urine volume during the disease course. Her past medical record was notable for a 3-year history of hypertension, for which she took intermittent irbesartan and beta-blockers and was considered to be well controlled. She reported no history of diabetes mellitus or long-term use of medications except the ones reported above. She had no history of alcohol use or potentially nephrotoxic medications. There was a slight increase in her menstrual blood volume over three past years. The patient had a 10-year-old daughter and reported no known family history of gout. Her parents underwent routine health examinations every year, and neither had obviously elevated SCr or sUA. On physical examination after admission, the patient had a blood pressure of 148/88 mmHg and a heart rate of 70 beats per minute. She was obese, with a body mass index of 32.8 kg/m^2 . The skin of her left ankle was red, tender, and the joint was swollen and unable to move. Numerous non-tender solid nodules were spotted on her hands, feet, and her right auricle. The fifth proximal interphalangeal joint of the right hand had flexion deformity.

During an evaluation at our hospital, laboratory tests revealed that she was moderately anemic. Her SCr was 220 $\mu\text{mol/L}$ (eGFR 25 mL/min per 1.73 m^2), and sUA 847 $\mu\text{mol/L}$. The serum triglycerides were 1.84 mmol/L. The results of urinalysis revealed urinary specific gravity of 1.007 and low pH of 5.0, while the urinary sediment analysis was overall normal. Her urinary osmolarity was 278 mOsm/kg H_2O . Her 24-h urine volume was 2500 mL, and fractional excretion of uric acid (FEUA) was 3.8%. Erythrocyte sedimentation rate was 40 mm/h. Ultrasonography of her urinary tract showed slightly shrunk kidneys (long axis: left 8.9 cm, right 8.6 cm) with a slightly hyperechoic cortex. Dual-energy computed tomography of

Access this article online

Quick Response Code:



Website:

www.cmj.org

DOI:

10.1097/CM9.0000000000001174

Correspondence to: Yun Zhang, Department of General Internal Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100730, China
E-Mail: zhangyun10806@pumch.cn

Copyright © 2020 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2021;134(7)

Received: 11-04-2020 Edited by: Li-Shao Guo

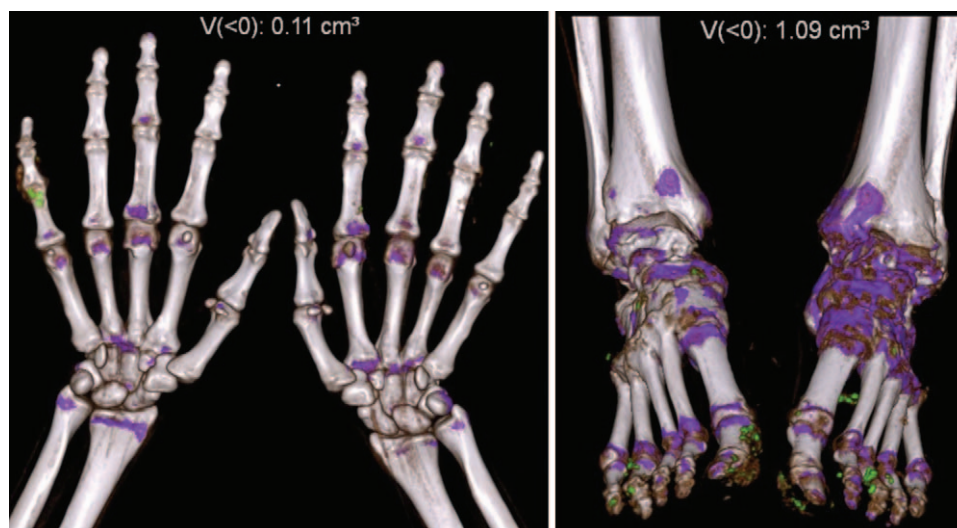


Figure 1: Dual-energy computed tomography documented green monosodium urate deposits on the patients' hands (left) and feet (right).

her hands, feet, and knees confirmed monosodium urate deposits [Figure 1].

Other potential causes for chronic arthritis and secondary hypertension were screened. Serum markers for rheumatoid arthritis, lupus, and vasculitis were negative. Total serum cortisol and adrenocorticotropic hormone were normal. Ultrasonography of renal arteries and adrenal glands were unremarkable. Therefore, rare genetic abnormalities were suspected; therefore, whole-exome sequencing (WES) of the patient was performed.

The patient was placed on a low-purine diet. She was instructed to drink copious water and take sodium bicarbonate to alkalinize her urine. Given her renal impairment, we were cautious about using non-steroid anti-inflammatory drugs, and decided to use the low-dose steroid for acute flares if necessary. She was initiated with 10 mg/day febuxostat oral treatment; the medication was well tolerated. Two weeks later, the dose of febuxostat was increased to 20 mg/day. She was prescribed nifedipine for hypertension and iron supplement for iron deficiency anemia. Her symptoms were controlled, and SCr and sUA were gradually improving (SCr 191 $\mu\text{mol/L}$, sUA 674 $\mu\text{mol/L}$ before discharged). The patient continued follow-up at the outpatient clinic.

A WES suggested a heterozygous mutation of the uromodulin (*UMOD*) gene (c.586G>T, pD196Y). The same mutation was also identified in her daughter, who was also tested for kidney function (her results were normal except for an apparently elevated sUA of over 600 $\mu\text{mol/L}$). Therefore, a diagnosis of autosomal dominant tubulointerstitial kidney disease (ADTKD) was made.

One month after discharge, the patient's joints symptoms improved. Her HGB returned to 115 g/L, sUA was lowered to 336.9 $\mu\text{mol/L}$, and her renal function slightly improved (SCr 194.9 $\mu\text{mol/L}$). Six months after discharge, she reported shrinking of tophi (over 50% smaller), yet she was kept on medications for over a month. During the last

follow-up, HGB dropped again to 83 g/L, SCr increased to 222.3 $\mu\text{mol/L}$, and sUA escalated to 781.2 $\mu\text{mol/L}$. The patient was re-instructed on the importance of continuous disease management and resumed her treatment.

ADTKD-*UMOD* (OMIM: 191845) is a rare autosomal dominant genetic abnormality caused by *UMOD* mutation. Patients with ADTKD-*UMOD* are characterized by low FEUA, early-onset gout, interstitial nephropathy, and progressive renal impairment, and they usually have a positive family history. Encoded by the *UMOD* gene on chromosome 16p12.3, uromodulin is produced by the cells of the thick ascending limb of the loop of Henle, which helps to maintain the integrity of the thick ascending limb and protects the kidneys from injury and inflammation.^[1] Mutations of uromodulin lead to defective protein maturation, pathogenic retention in the endoplasmic reticulum, and, therefore, progressively deteriorating nephropathy.^[2]

The same D196Y mutation was previously reported in a Latvian family with a distinctive family clustering pattern.^[3] Although positive family history is one of the most important clues, no family members of our index patient have reported a history of gout or CKD. Yet, previous literature on the rare early-onset gout in females suggested a higher likelihood of genetic abnormalities, including ADTKD, which is consistent with the very early disease presentation, and the unusual severity.^[4] The importance of genetic screening in premenopausal female gouty patients should be highlighted.

No "perfect" cure is currently available for ADTKD-*UMOD*. Few treatment strategies for facilitating uromodulin maturation and decreasing endoplasmic reticulum stress have been proposed, most of which are still under investigation.^[5] However, many strategies have been proposed to slow down disease progression and improve quality of life. In this patient, brief discontinuation of medications led to a visible increase of SCr and sUA, which stressed the importance of comorbidity control. If left untreated, they could further deteriorate the condition.

Therefore, the patients should be instructed on lifestyle modifications and regular use of urate-lowering medications. Monitoring and management of concomitant metabolic abnormalities are also crucial.

An awareness of possible genetic abnormalities should be emphasized in young females with gout. In our patient, the UMOD mutation has rendered lifelong disease management necessary. Management of gout and other comorbidities, and avoidance of nephrotoxic medications can improve the quality of life and slow down the progression of CKD. Noticeably, the daughter of our index patient carries the same mutation, and she developed hyperuricemia at a much younger age. Although she had no signs of arthritis, and her SCr was within the normal range, her clinical and laboratory parameters should also be closely monitored. Also, if she should decide to get pregnant in the future, prenatal diagnosis is highly recommended.

Declare of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for his images and other clinical information to be reported in the article. The patient understands that her name and initials will not be published and due efforts will be made to conceal the identity of the patient, although anonymity cannot be guaranteed.

Funding

This work was supported by grants from the Capital Medical Development Research Fund (No. 2018-1-4012),

the National Natural Science Foundation of China (No. 81901667).

Conflicts of interest

None.

References

1. El-Achkar TM, Wu XR, Rauchman M, McCracken R, Kiefer S, Dagher PC. Tamm-Horsfall protein protects the kidney from ischemic injury by decreasing inflammation and altering TLR4 expression. *Am J Physiol Renal Physiol* 2008;295:F534–F544. doi: 10.1152/ajprenal.00083.2008.
2. Williams SE, Reed AA, Galvanovskis J, Antignac C, Goodship T, Karet FE, *et al.* Uromodulin mutations causing familial juvenile hyperuricaemic nephropathy lead to protein maturation defects and retention in the endoplasmic reticulum. *Hum Mol Genet* 2009;18:2963–2974. doi: 10.1093/hmg/ddp235.
3. Lhotta K, Gehringer A, Jennings P, Kronenberg F, Brezinka C, Andersone I, *et al.* Familial juvenile hyperuricemic nephropathy: report on a new mutation and a pregnancy. *Clin Nephrol* 2009;71:80–83. doi: 10.5414/cnp71080.
4. Medeiros MM, Silva GB Jr, Daher EF. Tophus gout and chronic kidney disease in a young female patient: report of familial juvenile hyperuricemic nephropathy in three generations of the same family. *Rheumatol Int* 2012;32:3687–3690. doi: 10.1007/s00296-011-2106-5.
5. Kemter E, Sklenak S, Rathkolb B, Hrabec de Angelis M, Wolf E, Aigner B, *et al.* No amelioration of uromodulin maturation and trafficking defect by sodium 4-phenylbutyrate in vivo: studies in mouse models of uromodulin-associated kidney disease. *J Biol Chem* 2014;289:10715–10726. doi: 10.1074/jbc.M113.537035.

How to cite this article: Cao Y, Han XX, Wang XX, Zhang Y, Zeng XJ. Early onset gout and chronic kidney disease in a young female patient. *Chin Med J* 2021;134:854–856. doi: 10.1097/CM9.0000000000001174