Case Report

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Kelley-Seegmiller Syndrome: Urolithiasis, Renal Uric Acid Deposits, and Gout: What is the Role of the Urologist?

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Abstract
Kelley-Seegmiller syndrome (KSS) is a disorder that occurs when there is a partial deficiency of the enzyme hypoxanthine guanine phosphoribosyl transferase. It is involved in the metabolism of purines, clinically manifesting as hyperuricemia, hyperuricosuria, gout arthritis, and urolithiasis. The aim of this article is to present the case of a 33-year-old male with KSS, with left ureteral colic, and a 5-mm, 323-HU ureteral calculi, successfully managed with conservative management. It is critical to recognize that most urologists are not familiar with this inborn metabolic error and 75% of these patients will be affected by urolithiasis, thus making it a very critical and significant disease in our practice.

Introduction

Kelley-Seegmiller syndrome (KSS) is an X-linked recessive disease, with partial deficiency of the enzyme hypoxanthine guanine phosphoribosyl transferase (HPRT), an enzyme involved in the metabolism of purines. The biochemical hallmark of the disease is overproduction of uric acid, clinically presenting as chronic tophaceus gout, psychomotor development delay, urolithiasis, and chronic kidney disease (CKD) [1].

In 75% of the cases, urolithiasis is diagnosed before the age of 20, making it mandatory for the urologist to be familiar with this disease. The aim of our article is to present the case of a 33-year-old male with KSS who presented at the emergency department with acute ureteral colic, ureterolithiasis, and renal uric acid deposits and was successfully treated with conservative management [2, 3].

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Case Report

A 33-year-old male presented for the first time at the emergency department in February 2000 with psychomotor development delay, tophaceus gout at the right pinna, elbows, ankles, and gross deformities of all fingers and toes; the mobility of joints was restricted and he had developed multiple swellings around those joints. The uric acid level was abnormally high (11.9 mg/dL) and he was started on allopurinol and colchicine (Fig. 1).

In 2004, at 18 years of age, when he presented with bilateral renal uric acid deposits, (370 HU average) urolithiasis was ruled out. He also had developed megaloblastic anemia secondary to colchicine, the uric acid remain high (17 mg/dL) and the nephrologist suspended allopurinol and colchicine and started him on Febuxostat 120 mg daily. It was only after 12 years that he was suspected to have KSS and was ordered a purine (uric acid, hypoxanthine, xanthine, adenine, and guanosine) and pyrimidine (cytosine, uracil, cytidine, and tymine) high performance liquid chromatography. HPRT1 Xq26 sequencing showed a pathologic homozygous variant of the HPRT1 gene c.59A>T (Asp20Val) confirming the diagnosis of KSS in June 2017. This same year he presented with CKD stage 3 A1 with an eGFR of 51 mL/min/1.73 m^2 and with persistent abnormally high serum levels of uric acid and had an increase in the dose of Febuxostat to 200 mg daily.

In January 2018, he developed septic arthritis secondary to infected tophi at the left lower limb. During this hospital stay, he developed KDIGO 3 acute kidney injury (AKI) with a rise in the serum creatinine (sCr) levels of up to 6.9 mg/dL, requiring renal replacement therapy with hemodialysis. He was discharged with an sCr of 5.33 mg/dL and without the need for renal replacement therapy.

He presented a month later with an abrupt onset of colicky pain at the left flank irradiated to the lumbodorsal region with an sCR of 2.53 mg/dL, was suspected of having ureteric colic, and a CT scan documented a 5-mm, 323 HU calculi at the middle third of the left ureter associated to cystolithiasis, bladder calculi of 4 mm and 492 HU, bilateral uric acid deposits with 390 HU (average density) and intra-prostatic calcifications of 490 HU. All stones were not seen in plain KUB film (Fig. 2).

In conjunction with the nephrology team, we recommended conservative observational management because he did not have urinary tract infection, had good pain control with analgesics, the probability of spontaneous passage of the stone was high, and although he recently had an AKI KDIGO 3, the sCr continue to descend. He visited our clinics for the last time in March 2018 and a CT scan confirmed spontaneous passage of the ureteral stone and an sCR of 2.47 mg/dL (Baseline creatinine; Figure 3). He was ordered a complete metabolic evaluation, given that his ureteral colic has resolved. He visited us with the results in July 2018 with an sCR of 2.43 mg/dL, sNa^+ of 141meq/L, sK^+ 4.6 meq/L, and sUric acid 8.2 mg/dL. The 24-h urine collection reported a urine volume of 2.3 L, urine pH 6.4, gravity 1026, calcium 180 mg/day, oxalate 38 mg/day, citrate 402 mg/day, and uric acid 850 mg/day. As part of the management of uric acid stones, we advised the patient to increase his fluid intake up to 2.5–3 liters per day and to perform urine alkalization with sodium bicarbonate and potassium citrate and to continue taking Febuxostat to prevent hyperuricemia and hyperuricosuria. When he performed the metabolic evaluation, he was receiving febuxostat 200 mg/day and potassium citrate 30 mEq/day and the serum uric acid and 24-h urine uric acid levels were slightly elevated without other metabolic derangements.

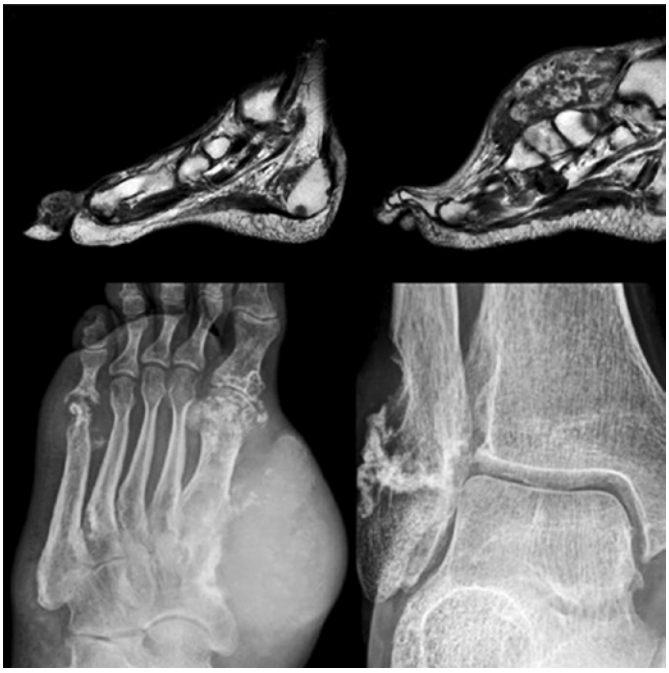

Fig. 1. Tophi deposited in and around meta-tarsophalangeal joints, proximal interphalangeal joints of all toes. Proximal and distal phalanx of all toes. Punched-out lytic lesions of the fifth toe meta-tarsophalangeal joint and the right fibula.

Discussion

KSS is a recessive X-linked disease and therefore, female carriers have only 1 copy of the mutation and do not express the inborn error of purine metabolism due to somatic cell mosaicism of HPRT activity and their sons are the ones who are usually affected. The partial deficiency of the enzymatic activity of HPRT was first described in 1967 by Kelley, Rosenbloom, Henderson, and Seegmiller. The exact prevalence of the disease is unknown, but it may represent about 15% of HPRT deficiency patients and it is often misdiagnosed as Lesch Nyhan syndrome (LNS) with a prevalence of 1/380,000 live births in Canada [1, 4, 5].

HPRT is a cytoplasmic enzyme that catalyzes the conversion of hypoxantine and guanine into inosine 5′-monophosphate and guanosine 5′-monophosphate. Phosphoribosyl-1-pyrophospate is used as a donor in the purine salvage pathway by inosine 5′-monophosphate or

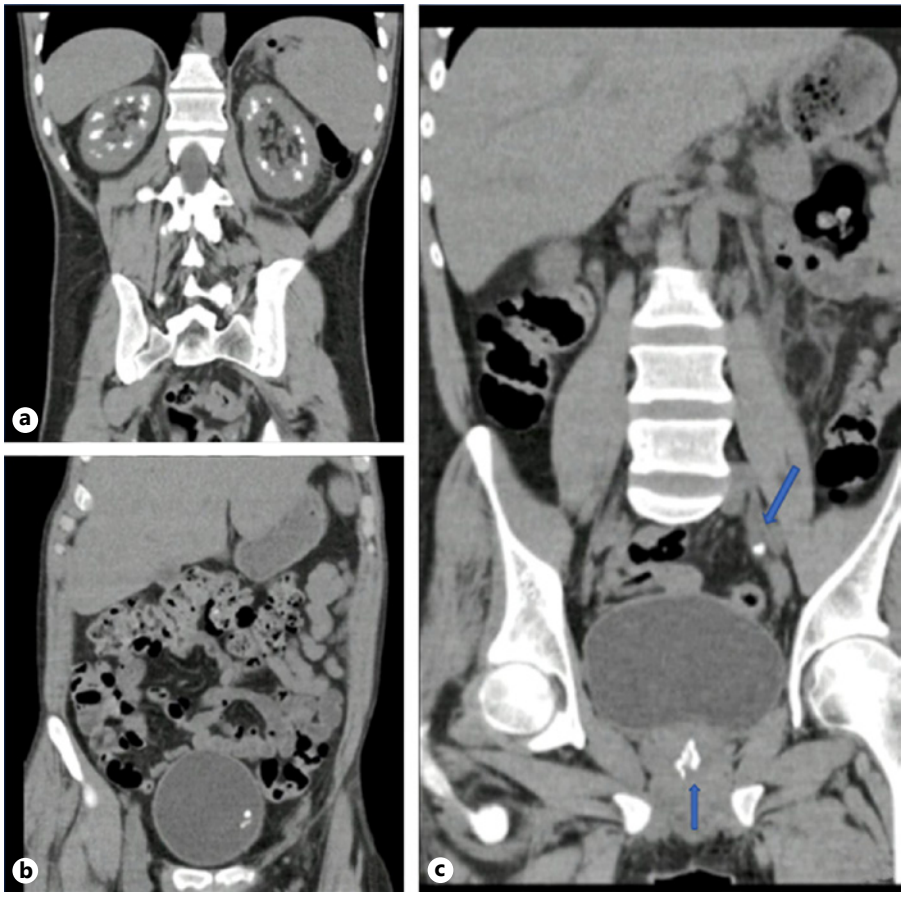

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Fig. 2. a Bilateral uric acid deposits, 390 HU (average density). **b** Cystolithiasis, 4 mm and 492 HU bladder calculi. **c** Left ureterolithiasis, 5 mm and 323 HU in the middle third of the ureter; intraprostatic calcifications of at least 4 mm and 492 HU.

guanosine 5′-monophosphate decreasing reutilization of purine bases and contributing to the accumulation of hypoxantine and guanine, enhancing de novo uric acid synthesis resulting in hyperuricemia, and hyperuricosuria [2, 4, 5].

The first manifestation of the disease may be the presence of orange-colored crystals or hematuria in the diaper. The clinical manifestations are based on the amount of residual HPRT activity, but usually all of the subjects have gouty arthritis, psychomotor delay development, and uric acid lithiasis. Urolithiasis is diagnosed in 75% of the patients before the age of 20; this is because serum uric acid levels in these patients can rise up to more than 18 mg/dL with a renal depuration of up to 16–36 mg/kg/day. They can also develop CKD and episodes of AKI secondary to interstitial deposits or tubular precipitation of uric acid crystals [8]. The neurologic impairment is dependent on the residual activity of the HPRT (Curto's theory) and therefore, less than 1.5% of activity is thought to result in classical LNS, which is characterized by self-mutilating and behavioral problems that are absent in KSS [1, 6, 7].

Differential diagnosis includes 6-phosphogluconate dehydrogenase deficiency, phosphoribosyl-1-pyrophospate synthetase superactivity, and LNS. The initial assessment must include serum and 24-h urine, uric acid levels, uric acid/creatinine ratio, purine (uric acid, hypoxanthine, xanthine, adenine and guanosine), and high-performance liquid chromatography. The diagnosis should be confirmed measuring erythrocytes or fibroblasts HPRT activity, with an enzymatic activity ranging from 0 to 10% in KSS and in the majority of cases, increased adenine phosphoribosyltransferase activity: The genetic diagnosis is made with HPRT1 Xq26 sequencing, confirming the mutation, which in most cases is a punctual mutation [2, 4].

The triad for uric acid stone formation is low pH, low urine volume, and hyperuricosuria, the latter defined as urinary uric acid excretion of more than 600 mg/day; this metabolic derangement predisposes to uric acid stone formation by causing supersaturation of urine with undissociated uric acid and increasing urinary levels of monosodium urate. This promotes heterogeneous nucleation with calcium oxalate crystals. Low pH is as

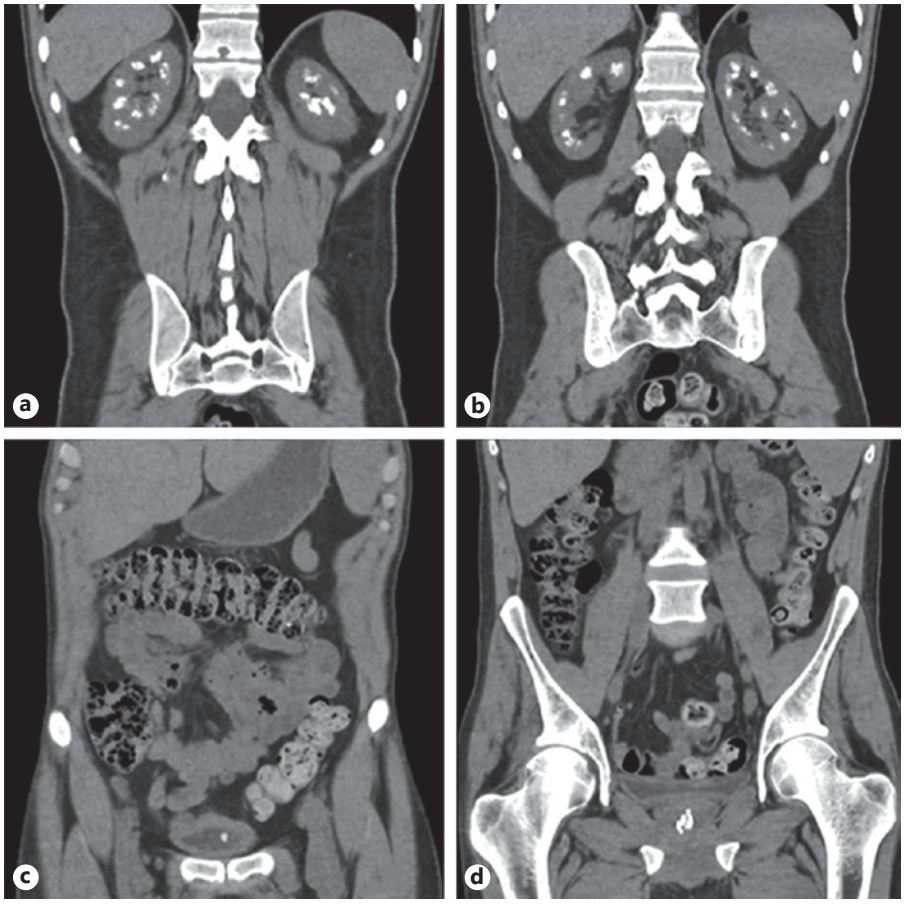

Fig. 3. a, **b** Bilateral uric acid deposits, 390 HU (average density). **c** Cystolithiasis, 5 mm and 323 HU bladder calculi, without evidence of ureteral calculi. **d** Intraprostatic calcifications.

important as hyperuricosuria, given that uric acid is a weak acid with a pKa of 5.35 at body temperature. At a pH lower than 5.35, modest increments of urinary uric acid, excess uric acid solubility and nucleation occurs. In KSS, the main problem is hyperuricosuria with urinary uric acid excretion exceeding 1,000 mg/day in most cases.

The mainstay of treatment in these patients is to reduce uric acid production with xanthine oxidase inhibitors such as Allopurinol or Febuxostat; alkalinizing the urine with potassium citrate (30–60 mEq/day) may raise urine pH from 5.5 up to 7.0 and improve the bioavailability of urine citrate. The last part of the treatment is to increase the fluid intake to achieve a daily urine output of at least 2 L. All these measures have been demonstrated to reduce the recurrence of urolithiasis and improve the quality of life of these patients [9, 10].

The role of the Urologist must be to become familiar with this disease, either to promptly identify it and be part of the diagnosis and initial assessment or to be part of the multidisciplinary management; urologists must be able to improve the quality of life, treat the episodes of ureteral colic and obstructive uropathy, and prevent the recurrence of urolithiasis and gouty arthritis-related complications. Future research should be conducted to describe the optimal management of the metabolic derangements of this disease. An effort should be made to include KSS in the urology practice guidelines and the management algorithm of patients with uric acid lithiasis to ensure that this condition no longer remains in the dark.

Ethics Statement

The patient in this manuscript has given his full written and verbal consent to publish photos and details of the case.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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