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Authors

Meagher, Margaret
Bechis, Seth

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Recurrent Xanthine Stones in a Young Patient with Lesch–Nyhan Syndrome

Margaret F. Meagher, BA[1] and Seth K. Bechis, MD, MS[2]

Abstract

Background: Lesch–Nyhan syndrome results from a rare X-linked inborn error of metabolism leading to a total body accumulation of uric acid. Clinical manifestations include self-mutilating behavior, poor muscle control, intellectual disability, gout, and kidney disease. Unfortunately, life expectancy is limited to the second or third decade of life because of symptoms associated with hyperuricemia, particularly renal failure. Patients with this condition frequently necessitate urologic intervention as the buildup of lithogenic substances predispose individuals to the development of kidney and bladder stones.
Case Presentation: We present the case of a 23-year-old white man with known Lesch–Nyhan syndrome and recurrent bilateral xanthine stones despite repeated urologic interventions.
Conclusion: Therapy for Lesch–Nyhan syndrome consists of reduction of uric acid achieved through allopurinol. However, excess allopurinol dosing can lead to development of xanthine kidney and bladder stones. Thus, the treating clinician must maintain a delicate balance between managing hyperuricemia and avoiding xanthine urolithiasis.

Keywords: Lesch–Nyhan, nephrolithiasis, xanthine, allopurinol

Introduction and Background

Lesch–Nyhan syndrome, originally described by William Nyhan in 1964, is characterized by a defect in the enzyme hypoxanthine guanine phosphoribosyl transferase (HPRT). As an X-linked recessive condition, Lesch–Nyhan deficiency affects mainly males with an estimated incidence of 1:100,000 to 1:300,000 live births in the US.[1]

HPRT performs a crucial role in purine metabolism, and deficiency produces an excess of uric acid with many systemic consequences.[1] The clinical phenotype of HPRT deficiency correlates with the degree of enzymatic insufficiency and ranges from nonapparent to Lesch–Nyhan syndrome, the most severe defect. Clinical manifestations of Lesch–Nyhan include central nervous system dysfunction with hallmark self-mutilating behavior, intellectual disability, and choreoathetosis. Hyperuricemia predisposes afflicted individuals to gout and a variety of kidney diseases such as urolithiasis and urate nephropathy. The mainstay of therapy includes allopurinol to lower the serum uric acid levels. Although only somewhat effective at reducing central nervous system symptoms, allopurinol is critical in modulating the equilibrium of serum uric acid and xanthine levels.

We present a case of recurrent xanthine stones in a 23-year-old white man with Lesch–Nyhan syndrome. Previous case reports have documented instances of xanthine urolithiasis in patients with Lesch–Nyhan; however, to date such reports have focused on pediatric patients.[2] We examine treatments for Lesch–Nyhan-associated urolithiasis as well as the challenges associated with allopurinol dosing.

Presentation of Case

The patient first presented to our clinic at the age of 21 after transitioning care from the local children's hospital, where he was initially found to have Lesch–Nyhan syndrome at 1 year of age after work-up for failure to meet developmental milestones. The patient had a prior extensive history of urolithiasis treated by pediatric urologists. Previous urologic interventions included bilateral ureteral stent placement, ureteroscopies with laser lithotripsy, and standard percutaneous nephrolithotomies (PCNLs) with documented complete removal of stones. Despite surgical and medical efforts, the patient continued to suffer from recurrent episodes of urolithiasis and pyelonephritis.

[1]Department of Urology, UC San Diego School of Medicine, La Jolla, California, USA.
[2]Department of Urology, Comprehensive Kidney Stone Center, UC San Diego Health, San Diego, California, USA.

At initial visit he was in a wheelchair with restraints given his history of self-injurious and impulsive behavior, but was verbal and interactive. He had previously completed high school on an individualized education plan. Medications included 750 mg allopurinol daily and 5 mEq potassium citrate twice daily. His urine chemistry at the time of presentation was significant for hypoxanthine of 892 mmol/molCr (normal <40 mmol/molCr) and xanthine of 334 mmol/mol Cr (normal <51 mmol/molCr) with uric acid below detectable limits.

CT scan demonstrated extensive bilateral urinary calculi with large renal stones at each ureteropelvic junction measuring 1.7 cm on the right and 1.3 cm on the left, as well as moderate to severe left renal obstructive hydronephrosis (Fig. 1). Renal function studies demonstrated a creatinine of 1.7, which was markedly elevated from his baseline of 0.8. Given this elevation, plan was made to proceed with cystoscopy and temporizing bilateral stent placement to be followed by staged PCNLs to preserve renal function.

However, urgent bilateral stents were placed after the patient was hospitalized with severe sepsis secondary to enterococcal pyelonephritis. He subsequently was hospitalized again with sepsis in the context of a Pseudomonas urinary tract infection. Throughout this time, serum uric acid was 1.2 mg/dL (normal 3.4–7.0 mg/dL). Kidney function normalized after relief of the obstruction.

He then underwent right standard (30 F) PCNL with stone analysis and culture. His postoperative course was complicated by sepsis requiring admission to the intensive care unit, and left standard PCNL was eventually performed during this hospitalization. Bilateral stone composition analysis was consistent with xanthine stones and follow-up CT scan showed no residual stone fragments. He was continued on 750 mg allopurinol daily with serum uric acid level of 0.8 mg/dL. One year later, the patient subsequently developed a recurrence of nephrolithiasis on the right consisting of two 11 mm stones of 260 HU and was scheduled for a ureteroscopy with lithotripsy. The stones were soft and were primarily dusted with basket extraction of a small number of larger fragments.

Postoperative CT scan after the most recent lithotripsy was significant for two right-sided stones measuring up to 9 mm. At last visit with urology, the patient was asymptomatic and reported passing stones without intervention.

At his most recent visit with the metabolic team, his physicians planned to reduce the dose of allopurinol to 10 mg/(kg·day) and titrate by uric acid measurement with goal uric acid around 3.5 mg/dL, within the low limit of normal. His allopurinol dosing was thus changed from 750 to 450 mg/day. Two months after dose modification, his repeat uric acid was 1.4 mg/dL. We do not have subsequent imaging after dose adjustments.

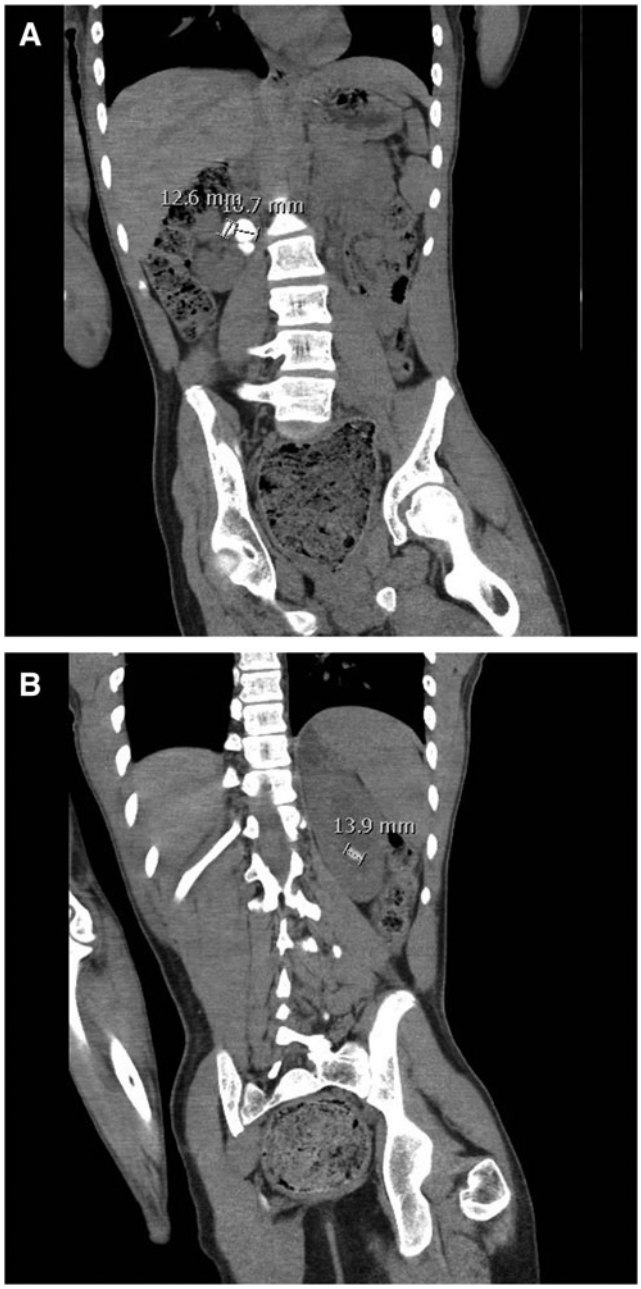

FIG. 1. CT abdomen/pelvis demonstrating multiple bilateral calculi with >4.2 cm of linear stone burden on the right **(A)** and moderate to severe hydronephrosis on the left **(B)**. The right kidney had average measured stone density of 265 ± 67 HU.

Discussion

Mutations in the HPRT gene leads to the hallmark hyperuricemia seen in Lesch–Nyhan syndrome.[1] HPRT dysfunction disrupts purine metabolism and results in the buildup of hypoxanthine, xanthine, and ultimately uric acid through the activity of xanthine oxidase. Systemic consequences of hyperuricemia include urate nephropathy, uric acid urolithiasis, formation of bladder calculi, and painful gouty arthritis.

Allopurinol, which inhibits xanthine oxidase, is a foundation of treatment for hyperuricemia. Allopurinol blocks the ability of xanthine oxidase to convert hypoxanthine and xanthine, products of purine catabolism, into uric acid, thereby lowering serum and urinary uric acid production. As a result, hypoxanthine and xanthine levels rise in the blood and urine. Xanthine is the least soluble of all purines naturally excreted in urine, and increased levels of urinary xanthine can lead to precipitation and stone formation.

The safety and efficacy of allopurinol in the treatment of hyperuricemia was demonstrated by Torres et al., who reported a mean reduction of serum uric acid by 47% and a mean reduction in urinary uric acid-to-creatinine ratio of 74%.[3] The authors also reported a 5.4-fold increase in

hypoxanthine and 9.5-fold increase in xanthine urinary excretion. Xanthine is poorly soluble in urine, which contributes to the increased risk of xanthine urolithiasis seen in patients treated with allopurinol.

Cameron et al. investigated the importance of close monitoring of allopurinol dosing, particularly in the context of Lesch–Nyhan syndrome.[4] The authors recommend a maximum dose of 5 mg/(kg·day) in children and 10 mg/(kg·day) in adults. Torres similarly emphasized the importance of dose monitoring, and recommend titration of allopurinol to maintain serum uric acid levels between 5.0 and 7.0 mg/dL—within normal range of laboratory testing—to prevent xanthine stone formation.[3]

The patient in our case presented with allopurinol dosed at 750 mg daily that had been increased with time in an effort to reduce urinary xanthine levels by inhibiting conversion from hypoxanthine. As the dose was increased, the patient had a corresponding decrease in urinary xanthine and uric acid levels with a slight increase in hypoxanthine levels, reflecting the increased inhibitory effect of allopurinol on xanthine oxidase. However, the overall urinary xanthine level still remained too high. These data suggest that the increased dosing of allopurinol dosing actually promoted a burden of recurrent stone formation so great as to be virtually refractory to intervention. Aggressive reduction of allopurinol dosing to maintain serum uric acid levels within normal range—but not so high as to cause neurologic symptoms—is critical to avoid tipping the scale from uric acid nephrolithiasis to xanthine nephrolithiasis.

With few treatments available for Lesch–Nyhan, it is important to find the balance of serum purine and uric acid levels to mitigate both neurologic and systemic side effects and the risk of stone formation. As our patient undergoes closer follow-up with the metabolic physicians, we hope that reduction in allopurinol dosing and maintenance of high-normal serum uric acid levels will prevent further xanthine stone formation.

Conclusion

Management of Lesch–Nyhan syndrome is complex and requires careful balance of serum uric acid and urinary xanthine levels. There is an ideal serum uric acid window above which predisposes to Lesch–Nyhan syndrome and below which leads to xanthinuria. Allopurinol must be titrated to maintain serum uric acid in the crucial window that alleviates the neurologic and systemic consequences of hyperuricemia while avoiding xanthine urolithiasis.

Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Seth K. Bechis, MD, MS
Department of Urology
UC San Diego Health
200 West Arbor Drive #8897
San Diego, CA 92103-7897
USA

E-mail: sbechis@health.ucsd.edu

Abbreviations Used

CT = computed tomography
HPRT = hypoxanthine guanine phosphoribosyl transferase
HU = Hounsfield units
PCNLs = percutaneous nephrolithotomies

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