An Unusual Case of Gout in a Young Woman with Gitelman Syndrome

To the Editor:

While gout is a very common and well-described disorder, it is rarely diagnosed in a young, premenopausal woman. Overall, men are more than twice as likely to develop this condition over their lifetime as women. This sex difference is at its greatest in the 20- to 49-year age group, where incidence is 1.3% for men versus 0.4% for women. The lower prevalence and incidence of gout in women has been attributed to the protective effects of estrogen and menstruation, which is consistent with the observation that it commonly manifests in women 10 to 15 years after menopause. When gout occurs in men under 30 years or in young women, investigation for a secondary cause is recommended. This investigation should include checking for acquired risk factors and genetic disorders that exacerbate hyperuricemia (Table 1).

A 27-year-old woman was referred by a nephrologist for chronic and intermittent right first toe pain, redness, and swelling for the past year. It was exacerbated by tight shoes, and relieved with nonsteroidal antiinflammatory drugs (NSAID). She also reported several episodes of pain, swelling, and redness in both ankles over the past year. She was constitutionally well and denied fevers, weight loss, or night sweats. Further history revealed psoriasis (PsO) treated with ultraviolet light therapy. She reported heavy alcohol use over the past 3 to 4 years, with binge drinking, and was previously hospitalized for acute pancreatitis. More recently she was diagnosed with Gitelman syndrome upon presenting with 2 years of episodically elevated creatinine along with hyponatremia, hypokalemia, elevated bicarbonate, and borderline high calcium. A diagnosis of Gitelman syndrome was made by exclusion of other conditions causing electrolyte imbalance and metabolic alkalosis, such as primary hyperaldosteronism, vomiting, and drugs (diuretics or laxatives). Her bland urinalysis, normal renal ultrasound, and no family history of renal disease further helped rule out glomerular, parenchymal, and other genetic causes. Her electrolyte abnormalities were managed with fluid and electrolyte replacement.

Given that Gitelman syndrome follows an autosomal recessive genetic pattern, it was hypothesized that both her parents were likely carriers. Conformational genetic testing was not performed for a number of reasons; the large number of involved genes and mutations, familial genetic heterogeneity, and high cost all limit the practicality of a molecular diagnostic approach. However, to our knowledge there is no literature describing an association between Gitelman syndrome and gout, and therefore it is unclear how many levels of serum UA would be expected in this syndrome.

Historically, it has been accepted that thiazide diuretics increase net UA reabsorption indirectly through diuretic-induced volume depletion and activation of the RAAS system. More recent data suggest diuretics have a direct interaction on renal UA handling through the voltage-driven UA transporter, which is down-regulated in Gitelman syndrome. It is uncharacteristic to observe tophaceous gout in a young woman, a clinical presentation that should prompt rheumatologists to investigate a secondary cause. In our patient, there were many contributing factors that drove elevated UA levels and clinical development of tophaceous gout. Her risk factors included the thiazide-like effect of Gitelman syndrome, hyperuricemia, and this association. Gout is most commonly seen in older men and postmenopausal women, and has well-described risk factors. It is uncharacteristic to observe tophaceous gout in a young woman, a clinical presentation that should prompt rheumatologists to investigate a secondary cause.

To our knowledge, our case study highlights for the first time the association between Gitelman syndrome and gout. We identified Gitelman syndrome as a novel risk factor for the development of gout and provided early insights into the pathogenesis of its association with hyperuricemia. However, further investigation is warranted into the pathogenesis of Gitelman syndrome, hyperuricemia, and this association.

Research ethics board approval was not required for the publication of this case report.
LAURENCE RUBIN, MD, Division of Rheumatology, St. Michael’s Hospital, University of Toronto, Toronto, Ontario, Canada. Address correspondence to Dr. L. Rubin, Division of Rheumatology, St. Michael’s Hospital, Bond Wing 3-061, 30 Bond Street, Toronto, Ontario M5B 1W8, Canada. E-mail: rubin@smh.ca

REFERENCES

11. Choi HK, Mount DB, Reginato AM; American College of

Figure 1. The effect of thiazide diuretic on uric acid transport in the renal proximal tubule. Most of the filtered uric acid is reabsorbed through the URAT1 located on the apical/luminal membrane of renal proximal tubular cells. It functions to transport uric acid from the proximal lumen in exchange for intracellular anions. It is theorized that thiazide diuretics increase uric acid reabsorption through volume contraction and activation of the RAAS system. (1) Ang II acts on the sodium–hydrogen ion transporter in the proximal tubule to increase sodium reabsorption. (2) There is sodium-dependent entry of monovalent anions (such as lactate, pyruvate, β-hydroxybutyrate, and acetate) through the sodium–anion co-transporter that raises acidity in the renal tubule and increases intracellular anion concentration. (3) The increased intracellular anion concentration gradient drives reabsorption of uric acid through the URAT1. (4) OAT in the basolateral membrane transport uric acid into the renal capillaries by fueling anion exchange into the cell as it flows down its concentration gradient. (5) Through unclear mechanisms, OAT or other pathways are also involved in uric acid secretion by stimulating anion exchange into the proximal cell, or diuretic-induced direct inhibition of uric acid excretion by the uric acid transporters SLC17A3 and ABCC4. Continual stimulation of the URAT1 transporter and inhibition of secretion and excretion of uric acid leads to net reabsorption and in turn causes hyperuricemia. URAT1: urate transporter-1; Ang II: angiotensin II; OAT: organic anion transporters; RAAS: renin-angiotensin-aldosterone system.
