THE JOURNAL OF FAMILY PRACTICE

ONLINE EXCLUSIVE

GRAND ROUNDS

Recent onset of rash, dehydration, and nonbloody diarrhea in an elderly man

A taste disturbance and anorexia accompanied his other symptoms. How would you proceed?

Tahirah Tyrell, MD, MSc; Janet Gick, MD
Rochester General Hospital, Rochester, NY (Dr. Tyrell); Clinton Memorial Hospital/ University of Cincinnati College of Medicine Program, Wilmington, Ohio (Dr. Gick)

tahirah.tyrell@rochestergeneral.org

The authors reported no potential conflict of interest relevant to this article.

An 80-year-old Hawaiian man of Chinese ancestry arrives at the emergency department with diarrhea and dehydration. You are called to admit him for acute renal failure. On entering the patient's room, you note that he has a diffuse maculopapular rash and is wheezing.

Twenty-one months earlier, the patient suffered his first episode of gout. Since that time, he has been asymptomatic. Two months ago, his primary care physician obtained a uric acid level and found it elevated at 10.6 mg/dL. She started the patient on allopurinol 300 mg PO daily.

Twenty days ago (approximately 6 weeks after initiation of allopurinol), the rash developed along with generalized pruritus. The patient's primary care physician referred him to a dermatologist for skin biopsy, and he discontinued allopurinol 11 days ago.

Just in the past week, the patient began to experience a metallic taste in his mouth, as well as anorexia, malaise, chills, dysuria, and nonbloody diarrhea. He became nauseous and decreased his oral intake, which led to dehydration and progressive weakness.

Additional medical history

- The patient's medical history is significant for renal insufficiency, type 2 diabetes mellitus, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, chronic nasal allergies, benign prostatic hypertrophy, osteoarthritis, and gout.
- He is taking the following medications: fluticasone inhalant 110 mcg daily; fluticasone propionate one spray in both nostrils daily; montelukast 10 mg PO daily; irbesartan 300 mg PO daily; amlodipine 5 mg PO daily; glyburide 2.5 mg PO BID; triamterene/hydrochlorothiazide 37.5/25 mg PO QOD; albuterol 90 mcg 2 puffs q6h prn; terazosin 2 mg PO qhs; simvastatin 40 mg PO daily; azelastine 137 mcg 1 spray in both nostrils prn; meclizine 25 mg PO daily prn; fexofenadine 150 mg PO qPM; cyclobenzaprine 10 mg PO qhs prn; and hydrocodone/acetaminophen 5/500 mg 2 tabs PO daily prn.

Social history

- The patient recently arrived from Hawaii to visit his wife's family.
- He does not drink alcohol, but he smokes 4 cigarettes a day.

Review of systems

- A review of systems is negative for the following: fever, sick contacts, history of renal calculi, hemoptysis, ocular or ENT symptoms, history of hepatic disease, peripheral neuropathy, and neurologic symptoms.

Physical examination

- The patient is alert and cooperative.

CONTINUED

The current standard of care for AHS is to discontinue allopurinol, administer parenteral corticosteroids followed by oral taper, and offer supportive management.

- Temperature is 97.9ºF, blood pressure 110/52 mm Hg, pulse 112 beats per minute, respiratory rate 16 breaths per minute, oxygen saturation 96% on room air.
- Mucous membranes are dry.
- Auscultation of the heart is normal.
- Significant wheezing is present in bilateral lung fields, but requiring no use of accessory muscles during respiration.
- Abdominal exam is remarkable only for obesity.
- Trace pitting edema is present in both lower extremities.
- The maculopapular rash is diffuse and nonblanching. Scaling on the trunk, areas of erythema below the umbilicus, and coalescing macular lesions on bilateral lower extremities are present.
- Joints are not swollen or tender, and there are no tophi.
- There are no focal neurologic deficits, and deep tendon reflexes are normal.

Laboratory studies completed in the ED

- Blood urea nitrogen, 112 mg/dL; creatinine, 3 mg/dL; glomerular filtration rate (GFR), 22 mL/min (baseline ratio of blood urea nitrogen/creatinine, 36:1.57; baseline GFR, 43 mL/min)
- White blood cell count, 15 k/uL
- Hemoglobin, 14.3 g/dL; hematocrit, 43.6%; platelet count, 307/uL
- Alanine aminotransferase and aspartate aminotransferase, 177 and 139 IU/L, respectively
- Direct, indirect, and total bilirubin, 0.60, 1.19, and 1.79 mg/dL, respectively
- Serum eosinophils, 22% (normal <6%)
- Erythrocyte sedimentation rate, 50 mm/h.

Radiology

- Chest radiographs (posterior-anterior, lateral) show a bilateral process consistent with atelectasis or lung scarring.
- Noncontrast computed tomography (CT) of the thorax confirms parenchymal scarring but no acute process.
- Hepatic sonography reveals increased echogenicity of the liver parenchyma consistent with an acute hepatocellular process.
- Magnetic resonance imaging (MRI) of the abdomen shows a diffuse process in the liver with trace parahepatic ascites.
- Renal ultrasound shows bilateral renal cysts with no hydronephrosis or urolithiasis.
- Cardiac echocardiography reveals left ventricular hypertrophy but normal ejection fraction.
- Noncontrast CT (head) and MRI (brain) show an acute right frontoparietal cerebrovascular accident and an old lacunar infarct.

Dermatologist's report

- A skin biopsy reveals lymphocytic perivascular infiltrate with scattered eosinophils and mild spongiosis consistent with vasculitis.

Follow-up laboratory data

- Acute hepatitis panel is negative
- Uric acid, 13.8 mg/dL
- Urine eosinophils, 31% (normal <1%)
- Anti-neutrophil cytoplasmic antibody IgG, 1:40 mildly elevated (normal <1:20)
- Anti-nuclear antibody (ANA) IgG, none
- Glycosylated hemoglobin, 7.1%
- High-sensitivity C-reactive protein, 207.96 mg/L (>10 mg/L is very high)

In summary, this patient's erythematous rash is a biopsy-confirmed vasculitis. Additional findings are hepatitis, acute on chronic renal failure, eosinophilia, and leukocytosis.

Q What is your presumptive diagnosis?

A

Allopurinol hypersensitivity syndrome

Allopurinol hypersensitivity syndrome (AHS) is a diffuse vasculitis induced by a type III hypersensitivity reaction, possibly to oxypurinol, allopurinol's toxic metabolite. The exact

pathophysiology is unknown, but oxypurinol levels correlate positively with the risk of AHS.[1] Thiazides may increase oxypurinol levels.[2]

Signs and symptoms of AHS include fever, erythematous skin rash, eosinophilia, hepatitis, progressive renal insufficiency, and leukocytosis. Case reports have also attributed septic shock, myocardial infarction, and Guillain-Barré syndrome to AHS.[3-6] The incidence of AHS is 0.1% to 0.4% of patients treated with allopurinol; mortality approaches 25%.[1]

Q What are the diagnostic criteria for AHS?

A

Singer and Wallace have outlined diagnostic criteria for AHS,[7] the first being a clear history of exposure to allopurinol.

Second, the clinical profile usually takes one of the following forms:

- The patient exhibits at least 2 of the following major features: worsening renal function, acute hepatocellular injury, or a rash (toxic epidermal necrolysis, erythema multiforme, or diffuse maculopapular or exfoliative dermatitis) ***or***
- The patient exhibits just one of the major features and at least one of the following minor features: fever, eosinophilia, or leukocytosis.

Third, there is no history of exposure to another drug that may cause a similar clinical picture.

Q What is the accepted treatment for AHS?

A

Although there is no well-established treatment plan, the standard of care is to discontinue allopurinol, administer parenteral corticosteroids followed by oral taper, and offer supportive management. Desensitization protocols are difficult and hypersensitivity reactions may recur. Early withdrawal of steroids has been reported to result in recurrence of symptoms. However, no strong data exist for determining an optimal length of corticosteroid therapy, or the number of days that constitutes "early" withdrawal of steroids. Mortality is high, even with seemingly adequate treatment.

Q Which patients are most at risk for AHS?

A

Definite risk factors for AHS include recent onset of allopurinol therapy, the presence of HLA-B5801 allele in patients of Han Chinese and European ancestry, and chronic kidney disease.[1,8,9] Suggested risk factors include concomitant use of thiazide diuretics with allopurinol, treatment of asymptomatic hyperuricemia, and high allopurinol dose relative to renal function.

Risk factors for AHS include recent onset of allopurinol therapy, HLA-B5801 allele in patients of Han Chinese and European ancestry, and chronic kidney disease.

Q What are the indications for allopurinol therapy?

A

Indications for allopurinol therapy:[1,10]

- Failure of uricosuric drugs or contraindications to their use
- Frequent attacks of gouty arthritis (≥3 per year)
- Nephrolithiasis
- Marked overproduction of urate, such as seen in tumor lysis syndrome
- The presence of tophi.

For patients with appropriate indications for allopurinol therapy, treat with the minimum effective dose. Initiation of allopurinol is controversial for a patient with a single lifetime episode of gout. However, most patients with one episode of gout will develop recurrent gout.[8]

In patients with creatinine clearance >60 mL/min, allopurinol is usually started

at 100 mg oral daily and titrated every 2 to 3 weeks until reaching the desired effectiveness.[8] One retrospective study suggests that initiating allopurinol at a dose of 1.5 mg per unit of estimated GFR may reduce the risk of AHS.[11]

Our patient's case: Treatment, discharge, readmission

With our patient, we started intravenous normal saline fluid boluses and parenteral methylprednisolone, 60 mg q6h. We discontinued triamterene/hydrochlorothiazide due to his hyperuricemia, and irbesartan and glyburide due to renal failure. Basal and rapid-acting insulins maintained good glycemic control. To control his wheezing and dyspnea, we began albuterol/ipratropium nebulizer treatments and oxygen delivery via nasal cannula. Nephrology, pulmonology, and rheumatology consultants agreed with these management decisions.

Over the next 9 days, the patient's renal function improved and his rash started to resolve. His wheezing fluctuated but persisted throughout the hospital stay. We stopped nasal oxygen delivery, and his oxygen saturation remained normal (96%-98%) on room air. He was subsequently discharged in stable condition on a 2-week prednisone taper starting at 30 mg bid.

Thirteen days later, he was readmitted with a right frontoparietal cerebrovascular accident (CVA). He developed respiratory distress, which led to respiratory arrest, and was ventilated. He became hypotensive, lapsed into shock, and died a few days later (approximately one month after initial presentation).

This case reminds us to be aware of the rare—but sometimes devastating—consequences of this commonly used drug.

The appropriate use of allopurinol—a second look

This case raised many questions for our inpatient team concerning not just AHS, but the appropriate use and dosing of allopurinol. Allopurinol is widely used for hyperuricemia and gout because it is effective for all causes of hyperuricemia and is inexpensive. Given that 3.9%[12] of the general population has gout and that its prevalence has increased with rising rates of obesity, the importance of AHS is not abstract.

Revisiting initial treatment choices. Our patient was at risk for this syndrome due to his Chinese ancestry, recent onset of allopurinol therapy, concomitant use of triamterene/hydrochlorothiazide, and impaired renal function. Although his uric acid level was >10 mg/dL when treatment was started, his risk factors may have precluded initiation of allopurinol. Furthermore, the prescribed dose of allopurinol (300 mg) was too high for his baseline GFR; 100 mg daily would have been more appropriate. It could be argued that hydrochlorothiazide would not be an antihypertensive of choice due to its hyperuricemic effects. Switching the thiazide to a loop diuretic would offer no benefit, because loop diuretics also cause hyperuricemia. (More on which antihypertensive agent would have been appropriate in a bit.)

The role of AHS in the patient's death is unclear. He was at high risk for stroke considering his age, comorbidities, and evidence of an old lacunar infarct. Myocardial infarctions have been reported as one cause of death in AHS, but we have found no reports of associated stroke. However, the temporal proximity of the CVA suggests a contributing effect of AHS. The adequacy of treatment is also brought into question. Early withdrawal of glucocorticoids can be associated with relapse of AHS; in retrospect, the prednisone dose may have been too low or the taper too short, or both.

Therapeutic alternatives to allopurinol were available. The most appropriate initial option for this patient likely was no pharmacologic intervention at all but a focus on weight loss and diet. The risk of gouty attacks in men increases as body mass index rises above normal (≥25 kg/m^2) and decreases with weight loss. Lower calorie diets with decreased saturated fat, higher complex carbohydrates, and allowed proteins (low-fat dairy products) are more palatable and more effective than strict low-purine diets.

A urate-lowering antihypertensive may have been a better option—specifically, losartan rather than irbesartan and triamterene/hydrochlorothiazide.[8,13] Losartan has uricosuric properties at the 50-mg dose.[14]

When compared in different studies with irbesartan, enalapril, and candesartan, losartan alone lowered serum urate levels. Increasing losartan to 100 mg could provide better hypertensive control but has not been found to lower urate levels more dramatically than the lower dose.[13]

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been found to blunt the urate-elevating effects of thiazides. Therefore, if the patient's blood pressure was not adequately controlled on losartan alone, the combination of losartan/hydrochlorothiazide would be a reasonable choice because minimal or no change in serum uric acid levels would be expected.[15]

Febuxostat, a nonpurine selective inhibitor of xanthine oxidase, is a potential alternative to allopurinol in patients with gout. It is a more potent urate-lowering agent than allopurinol and can be used without dosage reduction in mild (creatinine clearance [CrCl], 60-89 mL/min) to moderate (CrCl, 30-59 mL/min) renal insufficiency. Febuxostat is metabolized primarily in the liver—in contrast to allopurinol, which is excreted by the kidneys—and may increase liver transaminase levels.[10] Although febuxostat was not available at the time our patient developed AHS, it would not have been indicated in asymptomatic hyperuricemia.

This compelling case reminds us to carefully consider the indications and risk factors in using allopurinol, and to be aware of the rare but sometimes devastating consequences of this commonly used drug. JFP

CORRESPONDENCE
Tahirah Tyrell, MD, Rochester General Medical Group, 1425 Portland Avenue, Rochester, NY 14621; tahirah.tyrell@rochestergeneral.org.

Febuxostat, a nonpurine selective inhibitor of xanthine oxidase, is a potential alternative to allopurinol in patients with gout.

References

1. Lee HY, Ariyasinghe J, Thirumoorthy T. Allopurinol hypersensitivity syndrome: a preventable severe cutaneous adverse reaction? *Singapore Med J*. 2008;49:384-387.
2. Markel A. Allopurinol hypersensitivity and DRESS syndrome. *Am J Med*. 2008;121:e25.
3. Koike K, et al. Adverse reaction case reports. *React Wkly*. 2008 Sept 6;1218:5.
4. Mete N, Yilmaz F, et al. Adverse reaction case reports. *React Wkly*. 2004 June 26;1007:7.
5. Benito-León J, Porta-Etessam J. Guillain-Barré syndrome and allopurinol-induced hypersensitivity. *Eur Neurol*. 2001;45:186-187.
6. Makar-Ausperger KMA. Allopurinol/furosemide. Hypersensitivity syndrome: case report. *Reactions Wkly*. 2007 Oct 13;1173:5.
7. Singer JZ, Wallace SL. The allopurinol hypersensitivity syndrome. Unnecessary morbidity and mortality. *Arthritis Rheum* 1986; 29: 82-87.
8. Becker M. Prevention of recurrent gout. *UpToDate*. April 10, 2013. Available at: http://www.uptodate.com/contents/prevention-of-recurrent-gout?detectedLanguage=en&source=search_result&search=Prevention+of+recurrent+gout&selectedTitle=1%7E8&provider=noProvider. Accessed August 1, 2013.
9. Ramasamy SN, Korb-Wells CS, Kannangara DR, et al. Allopurinol hypersensitivity: a systematic review of all published cases, 1950-2012. *Drug Saf*. 2013;July 20. [Epub ahead of print].
10. Moreland LW. Febuxostat–treatment for hyperuricemia and gout? *N Engl J Med*. 2005;353:2505-2507.
11. Stamp LK, Taylor WJ, Jones PB, et al. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. *Arthritis Rheum*. 2012;64:2529-2536.
12. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum*. 2011;63: 3136-3141.
13. Würzner G, Gerster JC, Chiolero A, et al. Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricemia and gout. *J Hypertens*. 2001;19:1855-1860.
14. Terkeltaub RA. Clinical practice. gout. *N Engl J Med*. 2003; 349:1647-1655.
15. Manolis AJ, Grossman E, Jelakovic B, et al. Effects of losartan and candesartan monotherapy and losartan/hydrochlorothiazide combination therapy in patients with mild to moderate hypertension. Losartan Trial Investigators. *Clin Ther*. 2000;22:1186-1203.