ScieniQ Publishers

Archives of Clinical Case Studies and Case Reports

Case Study

Allopurinol Induced Hepatitis

Baraka Adam, Student-MD[1], Ezike Chinonso, MD[2], Afolake Mobolaji, MD, MPH, FAAFP[2]* and Folashade. Omole, MD, FAAFP[2]*

[1]Morehouse School of Medicine 720 Westview Dr, SW. Atlanta Ga 30310 404.756.1230

[2]Department of Family Medicine, Morehouse School of Medicine. 720 Westview Dr, SW. Atlanta Ga 30310Office 404.756.1230

***Corresponding author**
Afolake Mobolaji, MD, MPH, FAAFP. Assistant Professor, Clinical Family Medicine, Morehouse School of Medicine. 720 Westview Dr, SW. Atlanta Ga 30310.

Received: 14 June 2023
Accepted: 18 June 2023
Published: 24 June 2023

Abstract

Allopurinol is a xanthine oxidase inhibitor utilized in cases of gout and hyperuricemia. The drug has been linked to rare hypersensitivity reactions involving the integumentary and gastrointestinal systems. One of the most common organs involved in these cases of hypersensitivity reactions is liver transaminitis. Mindfulness in differentials of transaminitis and the workup approach is crucial in segregating the causes and effects of this patient's condition. In this case, we explore the management, prevention, risk factors, and exacerbating conditions in the cases of allopurinol hepatitis. In addition, our study emphasizes the importance of follow-up and screening of allopurinol-induced hepatitis.

Introduction

Allopurinol is a competitive inhibitor of xanthine oxidase indicated for gout secondary to hyperuricemia. It includes, but is not limited to, conditions of high cell turnover such as chemotherapy, cancer, and tumor lysis syndrome [1, 2], enzyme defects leading to hyperuricemia such as glycogen storage disease type I and Lesch-Nyhan Syndrome [3, 4], and asymptomatic hyperuricemia with comorbidities such as renal disease, hypertension, and hypercholesterolemia [4]. Allopurinol is given in initial 100 mg doses with 100 mg increments if needed, each week (with a <800 mg limit) until uric acid levels fall below 6mg/dl [1]. Side effects of allopurinol include GI distress, pruritis, ichthyosis, rash, fever, granulomatous hepatitis, and renal dysfunction [1, 2, 4]. There are few absolute contraindications of allopurinol, many of which include hypersensitivity reactions that can be exacerbated by high-risk genotypes (HLA- B * 58:01, HLA-B*53:01, and HLA-A*34:02) [5]. Among these include DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome, SJS (Steven-Johnson Syndrome), and TEN (toxic epidermal necrolysis). DRESS syndrome begins with a 2–8-week latency period of waxing and waning fever, rash, facial edema, lymphocytosis, eosinophilia, thrombocytopenia, and hepatitis [1, 6]. Interestingly, rash and fever can occur prior to liver injury, with eosinophilia being present after clinical manifestation [1]. SJS and TEN can present with similar symptomology; however, they include differing degrees of severe cutaneous reactions (SCAR) leading to epidermal skin sloughing. This usually presents as bullous lesions and, if extensive, can result in possible sepsis and mortality. Furthermore, as compared to DRESS, SJS and TEN may present with more mild transient signs of hepatitis [1, 7].

Allopurinol is discontinued in any systemic hypersensitivity reaction with end-organ damage, such as in hepatitis. Corticosteroids are sometimes administered to relieve symptoms such as fever and rash.[8] One caveat to this is in the case of cholestatic jaundice with hepatitis, in which corticosteroid use is not recommended. In addition, although corticosteroids can improve systemic symptoms, it is uncertain how effective corticosteroids are in reducing liver injury [1]. In this case, we explore allopurinol's relationship to transient transaminitis.

Case Study

A 66-year-old African American female with medical history of hypertension, recent diagnosis of gout, class 1 obesity, prediabetes, and mild renal insufficiency, presented to the emergency room with complaints of diarrhea and fatigue. She was recently started on allopurinol 100mg daily six weeks before her presentation. She reports two weeks of loose, watery, non-bloody diarrhea. Associated symptoms include fatigue, leg cramps, and light-headedness. She denies any fever or nausea/vomiting. She had no sick contact or recent travel, or use of laxatives. She also denies any history of alcohol use.

On examination, she was afebrile with a blood pressure of 109/62. Orthostatic vital signs were positive. She had dry mucous membranes and decreased skin turgor. Her abdomen was soft and non-distended, with mild right upper quadrant tenderness and mild hepatomegaly. She had bilateral shin tenderness to palpation. Normal findings were present during respiratory and cardiology exams except for mild tachycardia

Laboratory results revealed sodium = 123 mm/L, potassium = 3.2 mm/L, glucose = 97 mg/dL, anion gap 15, blood urea nitrogen = 61 mg/dL, serum creatinine = 2.09 mg/dL, alkaline phosphatase (ALP) = 450 IU/L, alanine aminotransferase (ALT) = 82 IU/L, aspartate aminotransferase (AST) =121 IU/L, white blood cells = 509000/mm3, platelet = 128000/mm3. Thyroid stimulating hormone = 2.43 IU/ml, SARS Cov-2 and influenza tests were negative. GFR was normal (>mL/min/1.73 m2). Hepatitis A, B, and C tests were negative. Significant medications include allopurinol.

CT abdomen/pelvis without IV contrast identified mild hepatomegaly without appreciable hepatic steatosis. Ultrasound gallbladder showed normal bile ducts and surgically absent gallbladder.

She was admitted for symptomatic hyponatremia and acute renal insufficiency. She was started on normal saline IV fluid, and her electrolytes were repleted. Her allopurinol was put on hold due to acute renal insufficiency and elevated liver function tests. Liver function tests trended up initially on day one of admission before trending down. Patient was discharged on day 3 with the recommendation to follow up outpatient for repeat labs. She was discharged home after hyponatremia correction and downward trending LFTs.

	Latest Reference Range & Units	03/02/22 08:57	03/03/22 01:56	03/03/22 12:13	03/04/22 02:03
ALKALINE PHOS	34 - 104 IU/L	482 (H)	561 (H)	543 (H)	509 (H)
AST	13 - 39 IU/L	111 (H)	122 (H)	103 (H)	80 (H)
ALT	7 - 52 IU/L	77 (H)	85 (H)	83 (H)	75 (H)
BILIRUBIN, TOTAL	0.0 - 1.0 mg/dL	1.9 (H)	1.8 (H)	1.5 (H)	1.1 (H)
GGT (GGTP)	9 - 64 IU/L	210 (H)			

DISCUSSION

Our patient initially presented with dehydration secondary to diarrhea, which was most likely allopurinol induced. In a meta-analysis by Luo et al. 2022 evaluating the effects of allopurinol on the renal function of diabetic patients, three trials reported adverse events that included diarrhea.[9] In a qualitative study assessing the prevalence of diarrhea and drug use in the elderly conducted by Pilotto et al. 2008, diarrhea was significantly associated with allopurinol use (OR 2.19, 95% CI 1.26–3.81) after accounting for baseline characteristics [10].

The transaminitis presented within our patient (defined as AST/ALT x 2 of normal limit) was most likely augmented by prerenal insufficiency from dehydration secondary to diarrhea. Allopurinol's metabolite, oxypurinol, a reactive oxygen species, is frequently elevated in patients with renal insufficiency, although not measured, may have compounded the elevation of our patient's LFTS. Other concerns of transaminitis secondary to allopurinol may be due to a latency period. In drug-induced liver injury, latency periods may last from a few weeks to a few months, including late LFT elevation and presentation9. Interestingly, the allopurinol latency period is described as 1-4 weeks, so her LFTS may have been elevated earlier (as her course started six weeks ago). Yet, liver injury from allopurinol is usually self-limiting after medication withdrawal, with a resolution in 7-10 days. Our patient's AST and ALT were found to normalize only after three days. In our management, to determine the cause of hepatitis, we conducted a hepatitis panel and reviewed our patients' other medications. However, tests were within normal limits. Possible causes for transaminitis include alcoholic liver disease, fatty liver disease, medication induced-hepatitis, thyroid disease, hemolysis, bilirubin excretion & conjugation irregularities, autoimmune hepatitis, and a1-antitrypsin deficiency. In our patient, part of the elevation of our LFTS may be due to non-alcoholic fatty liver disease as the patient had class I obesity. It is most likely that allopurinol was the culprit of transaminitis, as withdrawal led to decreased LFTs. If transaminitis persisted, we might have considered a liver biopsy which may have shown granulomatous inflammation due to hepatitis.

Even though ALP remained elevated. Causes of elevated ALP include cholestatic injury such as primary sclerosing cholangitis, tumor of the bone, metastatic disease. hyperthyroidism, hyperparathyroidism, granulomatous hepatitis, and non-granulomatous hepatitis, such as Wilson's disease and autoimmune hepatitis. To evaluate for this, we conducted a RUQ -ultrasound and a CT abdomen and pelvis. There was no evidence of bile duct dilation and inflammation. It is possible that using a more sensitive method such as MRCP may have viewed some dilation or inflammation regarding bile duct injury, which may have explained the elevated ALP [11]. Much of these cases are usually self-limiting. Few reports exist of life-threatening allopurinol liver injury [1].

In future directions, it would be interesting to explore the screening test and dosage guidelines to determine the risk of transaminitis in allopurinol depending on compromising medical conditions (such as pre-existing hepatitis, kidney disease, hyperthyroidism, autoimmune disease, and diabetes). In addition, further studies are warranted to elucidate comorbidities' effect on managing allopurinol-induced hepatitis.

DISCLOSURES

The authors report no relevant financial relationships.

References

1. In LiverTox: Clinical and Research Information on Drug-Induced Liver Injury (2012). National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda (MD).
2. Qurie, A., C.V. Preuss, and R. Musa, Allopurinol, in StatPearls (2022). StatPearls Publishing. Copyright © 2022, StatPearls Publishing LLC.: Treasure Island (FL).
3. Nanagiri, A. and N. Shabbir, Lesch Nyhan Syndrome, in StatPearls (2022). StatPearls Publishing. Copyright © 2022, StatPearls Publishing LLC.: Treasure Island (FL).
4. Li, L., Y. Zhang, and C. Zeng (2020). Update on the epidemiology, genetics, and therapeutic options of hyperuricemia. American journal of translational research. 12: 3167-3181.
5. Fontana, R.J., et al. (2021). Allopurinol hepatotoxicity is associated with human leukocyte antigen Class I alleles. Liver Int. 41: 1884-1893.
6. Choudhary, S., et al. (2013). Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome. The Journal of clinical and aesthetic dermatology. 6 6: 31-7.
7. Cho, Y.T. and C.Y. Chu (2017). Treatments for Severe Cutaneous Adverse Reactions. J Immunol Res. 2017: 1503709.
8. Iqbal, U., et al. (2017). Allopurinol-Induced Granulomatous Hepatitis: A Case Report and Review of Literature. J Investig Med High Impact Case Rep. 5: 2324709617728302.
9. Luo, Q., et al. (2022) Effects of allopurinol on renal function in patients with diabetes: a systematic review and meta-analysis. Ren Fail. 44: 806-814.
10. Pilotto, A., et al. (2008). The prevalence of diarrhea and its association with drug use in elderly outpatients: a multicenter study. Am J Gastroenterol. 103: 2816-23.
11. Walshe, T., et al. (2016). Imaging of the biliary tree: Infection, inflammation and infiltration. Applied Radiology. 45: 20-26.

Cite this article: Baraka Adam, Ezike Chinonso, Afolake Mobolaji and Folashade. Omole. (2023) Allopurinol Induced Hepatitis. Archives of Clinical Case Studies and Case Reports 4(2): 319- 320.