

Allopurinol inappropriate use in case of asymptomatic hyperuricemic patient causes fatal Allopurinol hypersensitive syndrome: lesson to allArvind Kumar^{1*}, Dinesh Kansal¹, Usha Kumari Chaudhary², Ajay Sharma³, Reena Sharma⁴

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ABSTRACT

Allopurinol is used to treat hyperuricemia (HU) in a patient of gout. It is also used to prevent HU in a patient of hematological malignancies who are about to undergo chemotherapy. Allopurinol is usually well-tolerated but it occasionally induces hypersensitivity reactions that manifest after few months of therapy. Cutaneous reactions are pruritic, erythematous, or maculopapular eruptions. Rarely fatal toxic epidermal necrolysis or Stevens-Johnson syndrome may occur. Transient leukopenia or leukocytosis, eosinophilia and elevated transaminases may also occur. HU is not a disease in itself. Its level is highly variable in the general population. Uric acid level is influenced by many factors such as dietary intake of proteins, hypertension, and obesity. Only very rarely patients of AHU may progress to gout and renal stones. Not much data is available that support HU alone in an asymptomatic patient in later life shows the diseases which are associated with HU. Sometimes only lifestyle changes, diet restrictions, alcohol restrictions, and treatment of underlying acquired cause may correct HU. Here, we are presenting a rare case of allopurinol hypersensitivity syndrome in an AHU patient. Our aim is to raise awareness among physicians so that they avoid using unnecessarily allopurinol in AHU patients and also titrate the dose of allopurinol in patients of renal failure. Risk-benefit ratio must be considered in these patients before starting allopurinol.

Keywords: Allopurinol, Allopurinol hypersensitive syndrome, Asymptomatic hyperuricemia

INTRODUCTION

Asymptomatic hyperuricemia (AHU) is a condition in which patient presents with high levels of serum uric acid without any sign and symptoms. HU is present in 5-30% of general population although prevalence is higher among

some ethnic group and seem to be increasing worldwide.¹ Almost 10% of adults are documented to have HU at least once in their lifetime.² HU is thought to be a risk factor for hypertension, cardiovascular disease and progression of renal injury,³ and metabolic syndrome.⁴ High levels of uric acid are an important risk factor in essential

hypertension and atherosclerosis.³ Uric acid is a final product of purine metabolism. So in routine baseline tests, serum uric acid level is actually not required. HU can be due to either increased production of uric acid, decreased excretion of uric acid or both. Hence, uric acid levels are mostly ordered in patients of acute monoarthritis, renal calculi, and toxemia of pregnancy.² Allopurinol is first-line drug for lowering serum uric acid level in patient of gout and is approved by the US-FDA.⁵ Allopurinol is the most common prescribed drug because of high efficacy and single dosing.⁶ Allopurinol inhibits xanthine oxidase and prevents synthesis of urate from hypoxanthine and xanthine. Allopurinol is used to treat HU in patients of gout. It facilitates the dissolution of tophi and prevents development or progression of chronic gouty arthritis by lowering the uric acid concentration in plasma below the limit of its solubility.⁶

CASE REPORT

A 46-year-old female patient a known case of hypertension, diabetic and chronic renal failure was found to be HU during follow-up incidentally, for which she was advised to take allopurinol 300 mg/day. After 1 month of initiation of allopurinol patient presented to the causality ward with signs and symptoms of fever, malaise, myalgia, pain abdomen and vomiting. Erythematous rashes first developed over the face along with edema and blackening and crusting of lips and upper limb (Figure 1). Later on these erythematous to maculopapular rashes spread over the chest, back and abdomen (Figure 2). These rashes were pruritic in nature.

Laboratory diagnosis

- Hemoglobin - 7.8 g%
- Total lymphocyte count - 34,600/ml
- Differential lymphocyte count - N₄₇ L₃₂ M₃ E₁₈ B₀ - showing eosinophilia
- Platelet count - 2,94000/mm³
- Serum glutamic oxaloacetic transaminase - 216 IU
- Serum glutamic pyruvic transaminase - 298 IU
- Alkaline phosphatase - 515 IU
- Serum sodium - 120 m Eq/L
- Serum potassium - 3m Eq/L.

Hematological microscopic picture showed microcytic hypochromic erythrocytes, eosinophilia that is increased eosinophils with reactive leukocytosis. Approximately, 35-40% of lymphocytes were ovoid with folded nucleus showing mild condensed chromatin with few of them showing prominent nucleolus. Features suggested drug hypersensitive reaction.

- Renal function tests - blood urea - 64 mg/dl
- Serum creatinine - 2.2 mg/dl
- Urine analysis - decreased volume



Figure 1: Shows odema of face along with blackening and crusting of lips with erythematous purpuric lesions



Figure 2: Shows atypical target-like or targetoid lesions spread over chest and abdomen of same patient.

- Large amount of protein
- Proteinuria 4 g/day
- Low serum albumin - 2.5 g/dl
- Hyaline and oval fat body casts in urine
- There was mild hepatomegaly present.

Test for hepatitis A and hepatitis B were negative. Tablet allopurinol stopped immediately. Further treatment included intravenous fluid, antihistaminies, analgesics, injectable antibiotics, intravenous dexamethasone and local anesthetic creams. Paraffin applied on lips to relieve pain. On day 15 after stopping allopurinol, patient's condition improved and patient discharged from the hospital.

Causality assessment as per Naranjo algorithm⁷ revealed adverse drug reaction score of 6 which come under probable category.

DISCUSSION

Allopurinol is used as uric acid lowering agent in gout, Lesch-Nyhan syndrome and in tumor lysis syndrome.⁶ Hence, it prevents the complication of HU.

Goal of therapy is to reduce plasma uric acid concentration to <6 mg/dl.⁶ Achieving sufficient reduction of uric acid serum levels may require 400-600 mg/day. In these AHU patients allopurinol therapy is still controversial. Allopurinol should be only very rarely be prescribe to patients with family history of gout and in patients with a very high level of uric acid because in this patient; there is high-risk of HU associated complications.² However, unfortunately allopurinol is prescribed very frequently for asymptomatic HU. In developing country like in India, most of the drugs are easily available as over the counter medicine.⁸ Allopurinol is one of the leading causes for the development of SJS/TEN. So allopurinol use should be restricted only in those patients in which it has establish indication for allopurinol therapy, and most importantly dose must be adjusted in renal failure patients.⁹

Maekawa et al.¹⁰ suggest genetic susceptibility with HLA-B*5801 for allopurinol-induced SJS and TEN. Screening of patients with HLA-B*5801 is a rapid and cost-effective method in these patients to prevent serious life-threatening SJS/TEN.

CONCLUSION

HU is not a disease in itself. Most of the time AHU patients never develop gout, renal stones and cardiovascular complications.^{1,2} In most of these patients HU can be treated by education, nutritional orientation and by lifestyle changes.¹ Even very large variation in uric acid level in society is present. Sometimes there may be other disorder associated with HU. So in these patients it is important to correct underlying acquired causes of HU.⁵ Kuo et al.¹¹ concluded that gout is independent risk for MI even in young people without any other cardiovascular risk factors. Palmer et al.¹² suggested that there is no strong association between uric acid and ischemic heart disease and in increase in blood pressure. In patients of asymptomatic HU lifestyle changes like weight loss, decrease purine rich meat, seafood and decrease alcohol intake help.^{2,13} The consumption of low-fat or non-fat dairy products is also beneficial.⁵ HU does not necessarily represent a disease state and it may be only a coincidently laboratory finding.² Even American guidelines for management of gout currently does not recommend urate lowering therapy for management of asymptomatic HU.⁵

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