Allopurinol: Sorrow to the marrow

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ABSTRACT

Allopurinol is a xanthine oxidase inhibitor used in management of chronic gout. It acts by reducing the amount of uric acid by inhibiting purine metabolism. A middle-aged hypertensive female who was on allopurinol for 7 months presented with generalized weakness and exertional dyspnea. Investigations revealed pancytopenia: normocytic normochromic anemia (Hb-3.2 g/dL, TLC-3400/mm³) and severe thrombocytopenia (Platelets-1000/mm³) with mild hepatosplenomegaly and grade 2 medico renal disease with normal cardiac status. Nutritional, hemolytic and infective causes were ruled out. She was transfused with fresh whole blood, platelets, administered empirical antibiotics and started on steroids. Initially, she responded to treatment but later developed an episode of convulsions with anuria and succumbed to leukopenic sepsis secondary to hypo/aplastic anemia probably due to allopurinol. Allopurinol is used extensively in the management of chronic gout and is well tolerated due to its safety profile. But we here report a case of allopurinol induced aplastic anemia leading to the demise of a patient. Allopurinol though safe needs careful monitoring.

Keywords: Allopurinol, aplastic anaemia, gout

Introduction

Allopurinol is a xanthine oxidase inhibitor used in the management of gout. It reduces uric acid by inhibiting purine metabolism. Despite being a good safety profile in a wide range of patients, it has been rarely known to cause major adverse effects such as bone marrow suppression.

Symptoms include fatigue, pallor, weakness, pharyngitis, fever, and chills which are signs of neutropenia.

Current Case

The case was taken only after obtaining institutional clearance and informed written consent from the patient and attenders in JJM Medical College, Davangere. A 65-year-old woman who is a known case of hypertension on Tab. amlodipine presented with pain in both the knees and was diagnosed with gout in May 2018 and was started on allopurinol in September 2018 when analgesics showed poor response. She was asymptomatic for 7 months and did not follow-up with the orthopedician. She noticed generalized weakness and breathlessness upon exertion on 25th May 2019. Clinically she had pallor, mild splenomegaly and hepatomegaly but no lymphadenopathy, and other systemic examinations were normal. On evaluation, the patient was found to have pancytopenia with normocytic normochromic anemia with severe thrombocytopenia (Hb-3.2 g/dL, TLC-3400/mm³, platelets-1000/mm³). On an emergency basis, she was resuscitated with packed cells, platelet transfusion, antibiotics, and methylprednisolone was also started.

Patient's platelet count improved to 54,000 and was discharged 2 days later on request, and was advised to take care to avoid any infection and report SOS if any bleeding occurs. Consequently, 4 days later, the patient presented with blood-tinged nasal discharge and watering of eyes. Patient's platelet count was 10,000 and was transfused 4 pints of platelets and was discharged on request on 31st May 2019.

On 4th June 2019 patient developed fever, ecchymosis in the right eye which progressed to both eyes, breathlessness, and anasarca with pain in both the knees and was diagnosed with gout in May 2018 and was started on allopurinol in September 2018 when analgesics showed poor response. She was asymptomatic for 7 months and did not follow-up with the orthopedician. She noticed generalized weakness and breathlessness upon exertion on 25th May 2019. Clinically she had pallor, mild splenomegaly and hepatomegaly but no lymphadenopathy, and other systemic examinations were normal. On evaluation, the patient was found to have pancytopenia with normocytic normochromic anemia with severe thrombocytopenia (Hb-3.2 g/dL, TLC-3400/mm³, platelets-1000/mm³). On an emergency basis, she was resuscitated with packed cells, platelet transfusion, antibiotics, and methylprednisolone was also started.

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The patient further developed 1 episode of convulsion and anuria. On 6th June 2019 patient still had anuria and platelet count of 1000 and was diagnosed to be in leukopenic sepsis and treated accordingly.

Investigations
On 26th CBC showed Hb-3.2, Rbc-1 million/mm3, TLC-3400/mm3, platelets-1,000/mm3, PCV-10.12, MCV-91.3, and reticulocyte count was 0.06% which improved to 0.1%, Peripheral smear showed pancytopenia with normocytic normochromic anaemia with severe thrombocytopenia and no abnormal cells. The thyroid profile was normal. vit B12- 588 pg/mL, folic acid 14 ng/mL, dengue, malaria, and Weil-Felix were negative. On 27th platelets-54,000/mm3. On the 5th CT brain showed chronic infarct in left gangliocapsular region, USG abdomen showed B/L grade II medico renal disease, and chest X-ray showed B/L pleural effusion. Besides, CBC showed Hb-7, Rbc-2 million/mm3, TLC-1810/mm3, platelets-12,000/mm3, serum sodium-119, potassium-3, chloride-87, calcium-7.9, RBS-164, urea-114, and creatinine-3.

Bone marrow aspiration was considered but could not be done due to the poor general condition of the patient.

Management
The patient was diagnosed as a case of hypoplastic/aplastic anemia probably secondary to drug-induced (allopurinol) because no other evidence suggestive of aplastic anemia was found. Besides, due to the acute presentation of the illness with the background of allopurinol intake for 7 months which has a known side effect profile of bone marrow suppression was considered.

The patient was transfused with packed cells, platelets, and also started on methylprednisolone. Empirical antibiotics were prescribed for sepsis. Phenytoin was added as antiepileptic. The patient was put on a ventilator owing to the development of septicemia and Multi-organ dysfunction syndrome (MODS) for 2 days but could not be revived and was declared dead on 9th June 2019.

Discussion
Allopurinol is used in the management of gout and is the first-line gout therapy at most of the centers due to its safety profile and cost. While the side effect profile of allopurinol is rare, they are severe and occur with an incidence rate of 1%. The mechanism is the generation of intermediate metabolites that bind to DNA and proteins to cause toxic effects on hematopoietic cells and genetic variability explaining the eccentric nature of drug-induced aplastic anemia. It is characterized by a latent period before the onset of anemia, continued bone marrow damage after drug discontinuation and dose independence. Multipotent hematopoietic stem cells undergo damage before their differentiation to committed stem cells. The number of circulating neutrophils, platelets, and erythrocytes is reduced.

Bone marrow suppression has been reported in patients treated with allopurinol. Most cases occurred in patients concomitantly using bone marrow suppressing drugs occurring as early as 6 weeks to 6 years in a few cases after initiation of allopurinol therapy.

In patients receiving allopurinol alone, cases of bone marrow suppression affecting more than one cell line have been rarely reported usually associated with predisposing factors such as chronic renal failure, malignancies such as leukemia, Hodgkin’s lymphoma, lymphosarcoma, and reticulosarcoma. However, this is a case with no such comorbidities wherein all the cell lineages were affected leading to aplastic anemia. Despite strict follow-up measures and blood count monitoring, this case proved to be a challenge resulting in the patient being refractory to any modality of treatment finally resulting in the death of patients secondary to sepsis.

Key Message
This case report is extremely relevant to primary care as we have to educate the patient regarding the side effects of allopurinol and the importance of follow-up with the physician regularly.

We have to repeat a complete blood count, renal function test, and serum uric acid level every 2 months if we are considering long-term therapy with allopurinol.

Allopurinol should be started only if the patient is symptomatic and if serum uric acid levels are elevated.
Alternative therapy with febuxostat should be considered. Febuxostat is a non-purine with selective xanthine oxidase inhibitor activity. It does not inhibit other enzymes in purine/pyrimidine synthesis or metabolism. It has got both hepatic and renal clearance thus can be given in patients with mild to moderate renal/hepatic patients with no dose modification. Hence might be a better option than allopurinol.

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**Conflicts of interest**
There are no conflicts of interest.

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