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CASE REPORT

Delayed hypersensitivity reaction to allopurinol: A case report

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Abstract

Allopurinol is the well-known first-line treatment option for symptomatic hyperuricaemia and gout. It is cost-effective particularly for the management of chronic gout. The common early side effects of allopurinol are skin rashes, diarrhoea and nausea. Meanwhile, a dangerous concerning complication is Stevens–Johnson syndrome, which can cause severe morbidity and mortality. Delayed hypersensitivity to allopurinol is rare but should be one of the differential diagnoses if a patient with underlying gout on chronic allopurinol treatment presents with skin rashes. The present case highlights the importance of a high index of suspicion in at-risk patients with underlying gout along with skin rashes on long-term allopurinol treatment to avoid unnecessary patient management.

Introduction

Allopurinol is used as a first-line remedy for hyperuricaemia and gout. It is a urate-lowering agent classified as a xanthine oxidase inhibitor.[1] This drug is highly recommended for patients with gout with one or more tophi, positive radiographic evidence of joint destruction, frequent attacks (i.e. two or more attacks annually) and urolithiasis.[2]

T cells play a pivotal role in mediated delayed hypersensitivities. Because hypersensitivity reactions comprise an immunological phase, the onset of symptoms varies between mild reactions and moderate and severe reactions. It typically takes 5–10 days from the first exposure until mild-to-moderate reactions, such as macular or maculopapular drug rash, fixed drug eruption and symmetrical drug-related intertriginous and flexural exanthema, occur. In contrast, life-threatening reactions, such as erythema multiforme-like eruption, Stevens–Johnson syndrome/toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms and acute generalised exanthematous pustulosis, occur on days 4 to ≥60 from the first exposure.[3]

Case presentation

A 35-year-old man was diagnosed with gouty arthritis since 2017. He had been on daily allopurinol treatment (600 mg) in the past 6 months and developed gradual-onset itchy skin lesions persisting for 2 months. The patient was initially treated with allopurinol at a low dose (100 mg) daily, which was increased slowly owing to uncontrolled gouty arthritis. His latest uric acid level was normal at 0.23 mg/dL, and his last gout attack happened in 2020.

Even after the patient visited a few general practitioners and received treatment for eczema and tinea, his skin lesions neither changed nor resolved and interfered with his daily activity. The skin lesions were itchy and localised on the upper back. He had no personal or family history of atopy or history of food or drug allergy. Because of the high index of suspicion for hypersensitivity, the case was discussed and evaluated with a dermatologist and consequently diagnosed as delayed hypersensitivity to allopurinol.

On examination, he was well and afebrile. His blood pressure was 120/80 mmHg, and his pulse rate was 70 beats per minute. There was no tophus formation seen. His back examination showed papules coalescing together to form an annular erythematous patch with central clearing and some scratch marks (**Figure 1**). There were no other lesions elsewhere. His blood investigations indicated normal findings.

Allopurinol treatment was stopped once delayed hypersensitivity was diagnosed, and cetirizine and Betnovate cream were prescribed. Within 2 days thereafter, his skin lesions gradually improved with complete resolution. He was then prescribed febuxostat at the rheumatology clinic.

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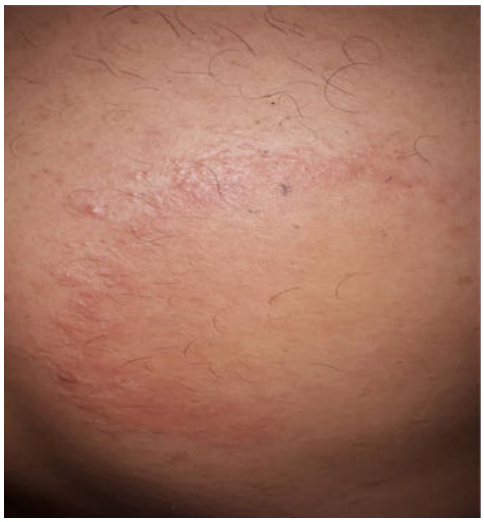

Figure 1. Skin lesions on the right upper back due to delayed hypersensitivity reaction to allopurinol.

Discussion

The factors that increase the risk of hypersensitivity reactions are female sex, age of ≥60 years, high initial drug dosage, renal disease, cardiovascular disease and asymptomatic hyperuricaemia.[4] In the present case, the patient diverges because he was a young man with no comorbidity and was initially on low-dosage allopurinol treatment. Hypersensitivity reactions probably occurred because the patient had a tenfold higher risk than a non-user of allopurinol.[5] As described, he was administered with 600 mg of allopurinol in the past 6 months to control the symptoms and achieve the target serum uric acid level. In general, the incidence of adverse cutaneous drug reactions is approximately 0.86% and ranges from 0.55% to 1.28% yearly.[6] An unclear drug history, medical history and unfamiliarity about allopurinol can also cause late diagnosis. Therefore, patient cognisance about allopurinol-related cutaneous reactions, such as rashes or itchiness, is essential when commencing therapy as well as the need to stop the medication when such reactions occur.[7] Thereafter, the dose must be started low and titred up to achieve the target serum uric acid level. This strategy mitigates the risk of adverse reactions.[2]

Tinea corporis may present a similar rash pattern: flat, red lesions progressing to annular lesions with central clearing.[8] Having a high index of suspicion for hypersensitivity reactions helps patients receive appropriate treatment. Complications, such as acute renal failure, pneumonitis, myocarditis and hepatitis, or mortality may occur in the absence of cognisance of hypersensitivity reactions, especially in patients with signs of bone marrow suppression and renal or liver impairment.[7]

Regarding management, allopurinol withdrawal and early treatment are critical for hypersensitivity reactions.[7] For symptomatic relief, topical corticosteroids are effective in managing mild-to-moderate drug reactions. Systemic corticosteroids may be added at a dose of 0.5–1.0 mg/kg/day if there is insufficient response. Antihistamines are also useful in the treatment of pruritus involving mast cells in type IV hypersensitivity.[3] Alternative prescriptions, such as biologic agents for cancer, TNF alpha-blockers for severe gouty arthritis and recombinant IL-1 receptor antagonists for chronic tophaceous gout, are also adopted to remediate the condition of patients with hypersensitivity to allopurinol. Febuxostat, a nonpurine selective xanthine oxidase inhibitor, has emerged as a potential alternative for preventing urate formation apart from allopurinol.[2] It has good efficacy and safety compared with other drugs, such as probenecid.[9] Gout may need long-term therapy to prevent further complications, including joint damage, long-term arthritis and renal stones.[2] In the present case, a rheumatologist prescribed febuxostat, which was well tolerated by the patient.

Conclusion

In conclusion, it is imperative to inform patients and healthcare providers about the possible delayed adverse effects of allopurinol. Consequently, early management can be initiated, and potential severe complications can be prevented.

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Conflicts of interest

None

Author contributions

Mohammad CM: As main supervisor of this case report, family medicine specialist interest in dermatology.
Shahidah CA: Giving opinion in discussion part and proofreading.
Wan Fatimah SWM: corresponding author, helping in managing this case, postgraduate student in family medicine.

Salman A: expert and opinion regarding allergic test and discussion.
Mohd Zhafri MR: family medicine specialist interest in dermatology, seen this case in clinic.
Rasimah Ismail: expert and opinion as dermatology specialist.

Patient's consent for the use of images and content for publication

The patient verbally consented to the use of his image and case for publication.

What is new in this case report compared to the previous literature?

- This case report highlights the importance of a high index of suspicion in at-risk patients with underlying gout along with skin rashes on long-term allopurinol treatment.
- After the initiation or uptitration of allopurinol treatment, awareness of hypersensitivity reactions is essential.
- Delayed hypersensitivity drug reactions cause unnecessary management and therefore should not be missed.

What is the implication to patients?

- Delayed hypersensitivity reactions can cause severe complications, but which can be prevented if such reactions are recognised early.

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