

# Allopurinol and Febuxostat Hypersensitivity in a Patient with Young Onset Gout: A Case Report

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## ABSTRACT

Gout is the most common inflammatory arthritis among Filipinos, characterized by hyperuricemia leading to monosodium urate crystal deposition and an ensuing inflammatory response. Though typically a disorder of middle-aged and older adults, tophaceous gout presenting before the age of 30 is rare and suggests aggressive disease progression. Allopurinol, a first-line urate-lowering therapy, is generally effective but may cause rare, potentially life-threatening adverse reactions such as allopurinol hypersensitivity syndrome (AHS). Febuxostat, a non-purine xanthine oxidase inhibitor, is an alternative for patients intolerant to allopurinol. Although hypersensitivity reactions to febuxostat are extremely rare, isolated case reports document their occurrence in both patients with prior AHS and in allopurinol-naïve individuals. Hypersensitivity to both agents is exceedingly uncommon and presents a major therapeutic challenge. In such cases, febuxostat desensitization, conducted in collaboration with allergy specialists, may permit a viable solution to safely reintroduce urate-lowering therapy and prevent further disease progression.

This case report describes a patient with young-onset, tophaceous gout who developed severe hypersensitivity reactions to both allopurinol and febuxostat — an unusual and challenging therapeutic dilemma. The case highlights the need for individualized management strategies, including the consideration of drug desensitization, in patients with limited urate-lowering options.

**Keywords:** gout, young onset gout, allopurinol hypersensitivity syndrome, febuxostat hypersensitivity, case report

## INTRODUCTION

Gout is the most common inflammatory arthritis among Filipinos.<sup>1</sup> It arises from hyperuricemia, leading to monosodium urate crystal deposition and a consequent inflammatory response.<sup>2</sup> Although typically seen in middle-aged and older men, the onset of gout before the age of 30, referred to as young onset gout, is uncommon and often indicates a more aggressive disease course.<sup>3,4</sup> Patients with young-onset gout are reported to have more frequent flares, earlier development of tophi, longer disease duration, involvement of multiple joints, and lower likelihood of achieving target serum uric acid levels.<sup>3,4</sup>

Urate-lowering therapy (ULT) is the cornerstone of gout management. Allopurinol, a xanthine oxidase inhibitor, has been the first line urate-lowering drug used for patients with gout.<sup>5</sup> However, allopurinol hypersensitivity syndrome, though rare, is a serious and potentially life-threatening adverse reaction.<sup>6</sup> Certain populations, particularly individuals of Korean, Han Chinese, and Thai descent, are at heightened risk for AHS due to genetic susceptibility, such as the presence of the HLA-B\*58:01 allele.<sup>7</sup> A population-based cohort study in Taiwan further highlighted this risk, reporting an overall incidence of allopurinol hypersensitivity at 2.7 per 1,000 users, compared to just 0.2 per 1,000 users

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for febuxostat.<sup>6</sup> Febuxostat, a non-purine xanthine oxidase inhibitor, is an alternative for those who are intolerant or have contraindication to allopurinol.<sup>8</sup> Hypersensitivity reactions to febuxostat have also been documented, both in patients with prior AHS and in those naïve to allopurinol, although such occurrences are exceedingly rare.<sup>8,9</sup>

## CASE PRESENTATION

We report the case of a 29-year-old Filipino male referred to the rheumatology service for chronic tophaceous gout. He had no known comorbidities. He was an occasional alcoholic beverage drinker, a 2 pack-year smoker, and had a prior history of methamphetamine use. He worked as a call center agent and had a strong family history of gout, with both his father and older brother affected. The patient experienced his first episode of gouty arthritis at 18 years old, presenting as podagra, which later progressed to episodic arthritis involving the ankles and knees. He intermittently took oral non-steroidal anti-inflammatory drugs (NSAIDs), which provided only temporary relief. At 23 years old, he began to develop visible tophi on both hands and feet, which eventually caused joint deformities and restricted movement. It was during this time that he was first prescribed with allopurinol at a dose of 100 mg daily. However, after one week of therapy, he developed generalized pruritus, facial swelling, painful erythematous papules, vesicles in the face and chest, and oral mucosal lesions. He was admitted and diagnosed with Stevens-Johnson Syndrome (SJS). Allopurinol was permanently discontinued, and he was treated with intravenous hydrocortisone and antihistamine, resulting in symptom resolution. Laboratory tests consistently showed markedly elevated serum uric acid levels ranging from 12 to 14 mg/dL (reference range 3.4-7.0 mg/dL). His previous serum creatinine levels were also elevated at 1.5 to 1.6 mg/dL (reference range: 0.7-1.2 mg/dL) with an estimated glomerular filtration rate (eGFR) of 55-59 ml/min, indicating mild renal impairment. Following the adverse reaction to allopurinol, the patient was lost to follow-up for two years. In his own words, he had not fully understood that long-term urate-lowering therapy was essential to control his disease and prevent complications. Additionally, the experience of Stevens-Johnson Syndrome left him fearful of experiencing another life-threatening drug reaction. As a result, he self-managed using oral prednisone (10 to 20 mg daily, as needed), which provided symptomatic relief but did not address the underlying hyperuricemia. Without urate-lowering therapy, the frequency of his gout flares increased up to ten times per year, necessitating almost monthly prednisone use. This was further complicated by episodes of infected, ruptured tophi requiring oral antibiotic treatment. Two years after the SJS episode, febuxostat was initiated at 40 mg daily orally as an alternative urate-lowering agent. However, after five days, he developed generalized pruritus and angioedema, requiring emergency care. Febuxostat was discontinued, and intravenous

corticosteroids were administered. A re-challenge with a lower dose of febuxostat (20 mg daily orally) was attempted one year later, but seven days into therapy, he again developed generalized urticaria. Discontinuation of febuxostat and a short course of prednisone 20 mg daily for seven days led to resolution of symptoms. Following this third hypersensitivity reaction, the patient was advised to consult the rheumatology service for further management.

At the time of rheumatology evaluation at the outpatient clinic, the patient had multiple tophi of the hands, elbows, knees, and feet (Figure 1). Laboratory workup showed a serum uric acid of 11.5 mg/dL, creatinine of 1.6 mg/dL, and an eGFR of 59 ml/min. His complete blood count, liver enzymes, urinalysis, and whole abdominal ultrasound were unremarkable. No significant diagnostic challenges were encountered, as the necessary laboratory tests to support the diagnosis were readily accessible and relatively free of charge through the outpatient clinic services at the Philippine General Hospital (PGH).

The patient was initiated on colchicine 0.5 mg daily orally as prophylaxis against acute flares. In addition to pharmacologic management, he received counseling on strict adherence to a low-purine diet and was advised to avoid common gout triggers such as alcohol, red meat, high-fructose beverages, and dehydration. However, since only allopurinol and febuxostat are available as urate-lowering medications in the country, and the patient had previously developed hypersensitivity reactions to both, treatment options were severely limited. Given the necessity of achieving sustained uric acid reduction to prevent further flares and progressive kidney damage, the patient was referred to the allergy service for febuxostat desensitization. This was carried out at another institution, where the patient was admitted for five days. A graded desensitization protocol was implemented, beginning with a 5 mg dilution preparation of febuxostat on the first day, followed by gradual dose escalation over five days under



**Figure 1.** (A) Multiple subcutaneous tophi over the dorsal and periarticular areas of the hand. (B) Ruptured tophus with overlying ulceration at the right first metatarsophalangeal joint, indicative of advanced tophaceous gout.

close monitoring. By the fifth day, the patient successfully tolerated a 20 mg febuxostat tablet without recurrence of hypersensitivity symptoms. He was subsequently discharged on febuxostat 20 mg daily and continued on outpatient follow-up for further dose titration toward the target serum uric acid level.

At three months post-desensitization, while on febuxostat 40 mg daily, the patient remained free of hypersensitivity reactions similar to his prior episodes. He experienced only one gout flare, which resolved with a 3-day course of oral prednisone 20 mg daily. Serum uric acid had decreased to 8.4 mg/dL, and febuxostat was up-titrated to 60 mg daily to further approach target urate levels. Reflecting on his journey, the patient shared that if he had known earlier about the option of febuxostat desensitization, and had been reassured that future drug reactions could be safely managed under specialist care, he would have sought rheumatology and allergy consultation much sooner. His case underscores not only the clinical challenges of managing a complicated case of gout but also the critical importance of patient education, health literacy, and shared decision-making in empowering individuals to pursue timely and appropriate care.

## DISCUSSION

Allopurinol hypersensitivity syndrome is a rare but potentially fatal, idiosyncratic, cell-mediated hypersensitivity reaction, with approximately 90% of cases occurring within the first 60 days of therapy.<sup>2</sup> Although the exact pathophysiology remains unclear, several risk factors have been identified, including the presence of HLA B58:01 allele, recent initiation of therapy, renal impairment, and concurrent diuretic use.<sup>6</sup> Febuxostat, a thiazolecarboxylic acid derivative, selectively inhibits xanthine oxidase by forming a stable complex with both the reduced and oxidized form. Its structural dissimilarity to allopurinol was thought to reduce the likelihood of shared hypersensitivity reactions.<sup>9</sup> However, reports of febuxostat-induced hypersensitivity, though rare, have since emerged. A population-based cohort study in Taiwan showed an overall incidence rate of allopurinol hypersensitivity at 2.7 per 1000 users compared to febuxostat hypersensitivity at 0.2 per 1000 users.<sup>6</sup> Nonetheless, febuxostat hypersensitivity reactions have been documented, and while generally considered rare, they can range from mild cutaneous eruptions to more severe presentations.<sup>10-12</sup>

Our patient, who developed severe hypersensitivity reactions to both allopurinol and febuxostat, illustrates a particularly challenging clinical scenario. The resolution of symptoms following discontinuation of both agents and administration of corticosteroids supported a drug-induced hypersensitivity mechanism. Importantly, the patient had underlying renal impairment, which likely contributed to his heightened risk of adverse drug reactions and complicated the choice of urate-lowering therapy. Adding further complexity to this case is the diagnosis of young-onset chronic tophaceous

gout, a relatively uncommon but increasingly recognized condition. Early-onset gout, typically defined as onset before the age of 30, represents a more severe form of disease, often associated with genetic predisposition, metabolic syndrome, renal insufficiency, and under-treatment.<sup>3</sup> Inadequate access to care or early urate-lowering therapy can accelerate disease progression, leading to the early formation of tophi, joint destruction, and significant morbidity. In such patients, the need for effective long-term urate-lowering therapy is urgent, particularly when advanced gout and tophi are already present.

The coexistence of hypersensitivity to both xanthine oxidase inhibitors, though rare, has been described in a few case reports. Evidence on the cross-reactivity between allopurinol and febuxostat remains conflicting. A retrospective study by Chohan et al. suggested that febuxostat could be safely used in patients with documented severe allopurinol reactions<sup>13</sup>, while a study by Bardin et al. reported a 10% rate of skin reactions in similar patients<sup>14</sup>, although true immunologic cross-reactivity was not confirmed.

Given our patient's need for ongoing urate-lowering therapy, the presence of tophaceous deposits, and a history of multiple gout flares per year, therapeutic intervention beyond dietary modification was essential. In the Philippines, the only available urate-lowering medications are allopurinol and febuxostat, both of which had previously triggered hypersensitivity reactions in this patient. As dietary changes alone were unlikely to achieve target serum uric acid levels in such a severe case<sup>15</sup>, and no alternative pharmacologic options were accessible, febuxostat desensitization was pursued. Reports of febuxostat desensitization in the literature are exceedingly rare and are mostly limited to case reports or small case series.<sup>11,12,16</sup> Indications typically involve patients with hypersensitivity to both xanthine oxidase inhibitors and no viable treatment alternatives.<sup>16</sup> Desensitization protocols are non-standardized but generally involve gradual dose escalation under close clinical supervision, often with the adjunctive use of corticosteroids and antihistamines.<sup>12</sup> Outcomes in published cases have been largely favorable, particularly among patients without a history of severe cutaneous adverse reactions. However, desensitization remains contraindicated in those with prior life-threatening reactions such as Stevens-Johnson Syndrome or DRESS<sup>17</sup>, therefore, desensitization to allopurinol was not attempted in this case.

Strengths of this case report include the detailed characterization of a rare and complex clinical situation, dual hypersensitivity to both first-line urate-lowering agents, in the context of young-onset chronic tophaceous gout. The case illustrates the practical challenges encountered in resource-limited settings and underscores the utility of febuxostat desensitization as a therapeutic option. Moreover, the report contributes to the scarce literature on febuxostat desensitization and may serve as a reference for clinicians facing similar dilemmas. However, several limitations should be acknowledged. The diagnosis of hypersensitivity was based



on clinical presentation and temporal association rather than confirmatory immunologic or pharmacogenetic testing, which were not feasible in this setting. Additionally, the desensitization protocol used was adapted from prior reports but not standardized, limiting its reproducibility. Follow-up duration was also relatively short, and long-term safety of febuxostat reintroduction remains unknown. Finally, as a single case report, the findings may not be generalizable to broader patient populations.

In our case, febuxostat desensitization was well-tolerated, with no recurrence of hypersensitivity symptoms during follow-up. This outcome highlights the potential utility of desensitization in carefully selected patients who are unable to tolerate first-line urate-lowering therapies due to hypersensitivity, resulting in inadequate treatment. It also reinforces the importance of a multidisciplinary, patient-centered approach in managing complex cases of advanced gout where therapeutic options are limited.

## CONCLUSION

Hypersensitivity to allopurinol and febuxostat is rare and presents a major challenge in treating young-onset chronic tophaceous gout. Febuxostat desensitization, in collaboration with an allergologist, can be considered as a viable therapeutic option for such cases. This approach underscores the critical need for interdisciplinary collaboration to develop individualized strategies for managing gout in patients facing these unique therapeutic challenges.

## Informed Consent

Informed consent was secured and patient confidentiality was observed.

## Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

## Author Disclosure

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