Reumatismo, 2023; 75 (3): 152-156

Acute severe gouty arthritis secondary to isotretinoin toxicity in a young male: a case report

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SUMMARY

Acute gouty arthritis is a recognized complication of hyperuricemia and one of the most common forms of inflammatory arthritis in adults. Drug-induced hyperuricemia is increasingly prevalent in clinical practice. Diuretics, antitubercular medications, and immunosuppressants are the common drugs associated with hyperuricemia. Oral isotretinoin is the drug of choice for different forms of severe acne and is rarely associated with hyperuricemia. We present the case of a 30-year-old male with severe acne vulgaris who was prescribed isotretinoin and later presented with acute gout. The patient developed hyperuricemia and swelling of the right first metatarsophalangeal joint within two months of isotretinoin commencement. There was a second episode of similar joint swelling three months later, parallel to the isotretinoin rechallenge. The dose of isotretinoin was reduced with the addition of febuxostat. The patient did not develop further episodes and remained symptom-free without urate-lowering therapy.

Key words: *Gout, arthritis, isotretinoin toxicity, acne, adverse effects.*

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INTRODUCTION

Gout is an inflammatory arthritis characterized by the deposition of monosodium urate (MSU) crystals in and around joints and the formation of tophi (1). It can present as acute monoarticular arthritis frequently affecting the first metatarsophalangeal (MTP) joint, recurrent gouty flares, or chronic tophaceous gout. Persistent hyperuricemia is a ubiquitous finding in gout; however, only a small proportion of hyperuricemic individuals (<5%) develops gout (2). In addition to hyperuricemia, gout may be favored by other risk factors like genetic predisposition (gene polymorphism), metabolic syndrome, dietary habits (high purine diet), malignancy (tumor lysis syndrome), and comorbidities (renal failure) (1). Drug-induced hyperuricemia is also recognized, with thiazides, ethanol, and ethambutol being the common culprits (3). Isotretinoin is a systemic synthetic retinoid used to treat severe acne. Cheilitis, xerosis, hypertriglyceridemia, and hypertransaminasemia are the most common adverse effects of isotretinoin use (4). Among musculoskeletal adverse effects, low back pain (with or without sacroiliitis) and tendinopathy are reported (5). Hyperuricemia secondary to isotretinoin use is rarely reported, especially in acute severe gout (6-8). We herein discuss the case of a young male who was prescribed isotretinoin for acne vulgaris and developed acute gout. We also highlight important aspects regarding the pathophysiology of hyperuricemia due to isotretinoin use.

CASE REPORT

A 30-year-old male presented with complaints of acute-onset severe joint pain of the right first MTP joint over 3 days. It was associated with swelling and erythema around the joint. There was no history of trauma, fever, or involvement of other joints. There was no similar episode documented in the past. Regarding his comorbidities, he had no current or past chronic

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illnesses except for acne vulgaris. There was no history of illicit drug use. He had been prescribed oral isotretinoin (45 mg/day) by his dermatologist for severe acne vulgaris 1.5 months earlier. There was no family history of gout, psoriasis, inflammatory bowel disease, or spondyloarthropathies. His height, weight, and body mass index (BMI) were 177 cm, 69 kg, and 22 kg/m^2, respectively. The physical examination was unremarkable except for the swollen and tender right first MTP joint.

Based on history and clinical examination, a suspicion of gout was raised, and laboratory investigations were ordered. The hemogram, kidney function test, and liver function test were within the normal limit (Table I). Among inflammatory markers, C-reactive protein was high (11.3 mg/L, normal <1 mg/L). His serum uric acid levels were significantly high (11.4 mg/dL, normal 3.5-7.2 mg/dL). No previous record of uric acid levels was available. Radiography of the right first MTP joint did not reveal any joint erosion or destruction. Synovial fluid analysis showed an increase in white blood cells (8000 cells/uL, 88% polymorphs); however, no evidence of crystals was found at microscopy. Synovial fluid gram stain and culture were negative. No evidence of other rheumatological disorders was detected. The patient was advised to take an anti-inflammatory drug (oral naproxen 500 mg twice daily for 7 days). In addition, he was also advised to take a short course of oral corticosteroids (prednisolone 40 mg in a tapering dose) for 10 days. The patient responded well, with resolution of local symptoms and signs. Urate-lowering therapy (febuxostat 40 mg OD) was advised one week later. However, the patient failed to follow up and stopped all medications, including isotretinoin. After 4 months, he developed once again a similar first MTP joint swelling for 2 days. Recently, isotretinoin was restarted (1 month previously) due to recurring acne. The patient's uric acid levels increased (10.9 mg/dL). Due to the variable sensitivity of MSU crystal identification in early gout, we advised the patient to repeat synovial fluid analysis, though the patient did

Table I - Hematological and biochemical indices during follow-up.

Laboratory variables	Day 1, when isotretinoin started, (normal range)	Day 38 (diagnosis of acute gout)
Hemoglobin (g/dL)	15.4 (14-16)	15.2
Total leukocyte count (cells/uL)	7460 (4000-11000)	8110
Platelets (cells/uL)	359000 (150000-450000)	343000
Hs-CRP (mg/L)	0.2 (<1)	11.3
ESR (mm/hr)	14 (0-20)	13
Serum uric acid (mg/dL)	Not available	11.4 (3.5-7.2)
ALT/AST (IU/L)	29/42 (<35)	25/51
TP/Alb (mg/dL)	6.75/3.57	8.4/4.7
T. bil/D. bil (mg/dL)	0.45/0.13	0.42/0.09
Creatinine/BUN (mg/dL)	0.36/26	0.45/11
Total cholesterol (mg/dL)	120 (<200)	145
HDL (mg/dL)	41 (>60)	38
LDL (mg/dL)	87 (<100)	104
Triglycerides (mg/dL)	154 (<150)	176
Rheumatoid factor (IU/mL)	Not available	10 (<14)

Hs-CRP, high sensitivity C reactive protein; ESR, erythrocyte sedimentation rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; ALB, albumin; T. Bil, total bilirubin; D. bil, direct bilirubin; BUN, blood urea nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table II - The Naranjo adverse drug reaction probability scale questionnaire.

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event occur after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	+2
5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	+1
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	0

Total = 9 (Definite)

The Naranjo criteria classify the probability that an adverse event is related to drug therapy based on a list of weighted questions, which examine factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, dose-response relationships and previous patient experience with the medication. The Naranjo adverse drug reaction is assigned to a probability category from the total score as follows: definite if the overall score is 9 or greater, probable for a score of 5-8, possible for 1-4, and doubtful if the score is 0. The Naranjo criteria do not take into account drug-drug interactions. Drugs are evaluated individually for causality, and points are deducted if another factor may have resulted in the adverse event, thereby weakening the causal association.

not provide consent. By applying the 2015 American College of Rheumatology-European League Against Rheumatism criteria (9), the patient was classified as having gout with a score of 11 points. The patient was again given a short course of naproxen and prednisolone. Febuxostat (40 mg) was introduced.

We tried to find out the possible cause of hyperuricemia. The patient did not have any predisposing factors for gout. Other differentials like septic arthritis (no history of fever, whole blood counts were normal, and synovial fluid analysis was negative for septic arthritis), osteomyelitis (no evidence in radio imaging), and rheumatological disorders (rheumatoid factor and antinuclear antibodies were negative) were ruled out. Since the patient did not take other drugs in the last two months and isotretinoin was

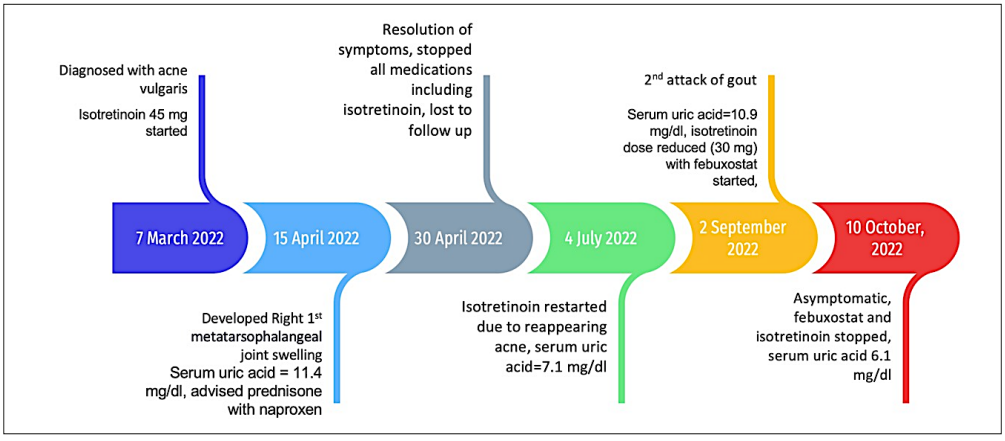

Figure 1 - Timeline of the development of gouty arthritis in relation to isotretinoin use.

started recently (4 weeks before), it was suspected to cause hyperuricemia and subsequent gout. We applied the Naranjo drug adverse reaction probability scale (10), which denoted a definite drug reaction to isotretinoin (total score=9 as reported in Table II). After the consultation with the dermatologist, the dose of isotretinoin was reduced to 30 mg once daily, which was completed in the next 2 weeks. Urate-lowering therapy was also stopped one month later. At 3 and 8 months of follow-up, the patient remains asymptomatic. The entire timeline of the clinical course is depicted in Figure 1.

DISCUSSION AND CONCLUSIONS

Acute severe gout is a debilitating disease that causes significant morbidity. Classically, it has been recognized as an inflammatory response secondary to MSU crystal deposition, resulting in a swollen big toe (podagra) (1). Identifying the underlying cause is sometimes challenging. In our patient, we ruled out other differentials like infections, trauma, and rheumatological diseases. He did not have any features of metabolic syndrome (diabetes, obesity, hypertension). We also did not find any renal dysfunction that could have caused reduced urate excretion and hyperuricemia. Only around 10% of cases of hyperuricemia are related to the endogenous production of uric acid (11). In this case, we identified isotretinoin as the probable cause/trigger for hyperuricemia and subsequent acute gouty arthritis. The patient developed acute gout in temporal correlation with isotretinoin therapy. Subsequent recurrence of symptoms was documented after the isotretinoin rechallenge; the patient only improved with the reduction of the isotretinoin dose and the addition of urate-lowering therapy. In 1998, Vanhootegham et al. published one of the earliest reports (8), describing an 80-year-old female with ischemic heart disease and psoriasis who developed hyperuricemia and gouty tophi after taking acitretin (35 mg). In that patient, serum uric acid was 17.1 mg/dL, and the acitretin dose was 0.49 mg/kg once daily (8). The authors could not find any other cause of hyperuricemia; however, how isotretinoin caused hyperuricemia remained unanswered. Karaosmanoğlu et al. described the musculoskeletal side effects of isotretinoin in patients with acne vulgaris (5). The drug was associated with the development of arthralgia, low back pain, sacroiliitis, and tendinopathy (5). However, none of the patients developed symptoms of gout. In 2012, Choi et al. conducted a national population study and concluded that serum retinol is independently associated with hyperuricemia (12). The pathophysiology of hyperuricemia and gout caused by retinol toxicity is debatable and still unanswered. The hypothesis proposed is the shared action of the xanthine oxidase enzyme in uric acid and retinol metabolism (7). There is an increase in xanthine oxidase activity owing to the increased availability of retinol, resulting in increased uric acid production (12). The ratio of retinoic acid to retinol can also help determine isotretinoin toxicity, which could be an area for further research. Another study by Solak et al. reported a significant increase in serum uric acid within two months of isotretinoin treatment (6). However, only one patient became hyperuricemic after the commencement of isotretinoin. Monocyte-high-density lipoprotein ratio (MHL) is a recently described inflammatory marker for atherosclerotic disease and metabolic syndrome. A recent report highlighted the linear correlation of MHL with hyperuricemia irrespective of age, gender, BMI, blood pressure, and low-density lipoprotein (13). MHL could be explored in patients receiving isotretinoin therapy, to predict the development of hyperuricemia. It is also more easily attainable compared to serum retinoic acid and retinol concentrations.

In conclusion, this report demonstrates the risk of hyperuricemia associated with isotretinoin therapy. It shows how much more research on gouty arthritis needs to be done. More studies are needed to establish the reported correlation. The other questions that need to be answered in isotretinoin toxicity are its relation to dose, ethnicity, genetic polymorphism, and other comorbidi-

ties. We recommend monitoring serum uric acid before and during isotretinoin therapy.

Contributions
DSM, DK, collected and analyzed the clinical data. All authors contributed to the study concept and design, drafted the manuscript, contributed to the literature search, and read and approved the final manuscript.

Conflict of interest
The authors declare no potential conflict of interest.

Patient consent for publication
The patient has given written consent for his personal and clinical details. The patient understands that his name and initials will not be published and that due efforts will be made to conceal his identity.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials
Data and materials are available from the corresponding author upon request.

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