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CASE REPORT

Agranulocytosis: an adverse effect of allopurinol treatment

Agranulocitosi: effetto avverso da allopurinolo

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KEYWORDS

Allopurinol;
Agranulocytosis;
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Summary

Introduction: Allopurinol is a xanthine oxidase inhibitor that is primarily used to treat hyperuricemia and its complications. The drug is rarely associated with adverse effects, but those that occur can be significant. Hematologic side effects, including bone marrow suppression, severe anemia, thrombocytopenia, and leukopenia, have been reported in 0.2-0.6% of treated patients. **Materials and methods:** We report a case of agranulocytosis associated with allopurinol therapy in a patient admitted for fever.

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Introduction

Drug-induced agranulocytosis, not associated with chemotherapy, is a rare adverse reaction characterized by decreased peripheral neutrophil counts to less than 0.5×10^3 cells/ μ L due to immunologic or cytotoxic mechanisms [1,2].

Allopurinol is primarily used to treat hyperuricemia and its complications, including chronic gout. Although allopurinol-induced agranulocytosis is uncommon, we report a case of a patient with agranulocytosis associated with allopurinol therapy.

Case report

A 90-year-old man with history of hypertension, chronic heart failure, chronic atrial fibrillation, mild chronic renal failure (creatinine clearance 30-40 mL/min), prostatic hypertrophy, and a recent diagnosis of esophageal adenocarcinoma was admitted to our department with fever. In the last six months, he had been hospitalized twice for heart failure. Home therapy included furosemide 125 mg twice daily, canrenone 50 mg/day, aspirin 100 mg/day, and dutasteride 0.5 mg/day.

After finding high levels of uric acid (11.4 mg/dL, normal value 3,4-7.0 mg/dL), treatment with allopurinol

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(100 mg/day) was started two months ago. At that time, her immune system functioned normally (white blood cell – WBC – count $9.28 \times 10^3/\mu\text{L}$, neutrophils $6.42 \times 10^3/\mu\text{L}$, lymphocytes $0.90 \times 10^3/\mu\text{L}$).

About 35 days after starting allopurinol therapy, laboratory exams found WBC count $5.91 \times 10^3/\mu\text{L}$, neutrophils $3.58 \times 10^3/\mu\text{L}$, and lymphocytes $0.90 \times 10^3/\mu\text{L}$.

Two days before hospital admission, the patient experienced asthenia and fever (38.9°C).

On admission, temperature (38.8°C), pulse (92 bpm, irregular for chronic atrial fibrillation), blood pressure (130/85 mmHg), and respiration rate (24 breaths/min) were elevated. Cardiovascular, respiratory, abdominal, and central nervous system examinations were normal. The patient had no physical limitations (Barthel's index: ADL 89/100; Braden's score: 19/22). Laboratory exams found WBC count $0.30 \times 10^3/\mu\text{L}$, neutrophils $0.01 \times 10^3/\mu\text{L}$, lymphocytes $0.24 \times 10^3/\mu\text{L}$, PCR 29.6 mg/dL, and creatinine 2.18 mg/dL. Blood, urine and stool cultures, carried out repeatedly, were always negative. Chest X-ray and abdominal ultrasound were normal.

Assuming an iatrogenic cause of agranulocytosis due to allopurinol, the drug was immediately discontinued, and therapy with antibiotics, hydration, and methylprednisolone 20 mg twice daily was started. The fever disappeared within 36 hours.

Six days after allopurinol discontinuation, the WBC count progressively increased (fig. 1).

After 8 days, the patient was discharged with usual therapy (furosemide 125 mg twice daily, canrenone 50 mg/day, aspirin 100 mg/day, dutasteride 0.5 mg/day); in addition, a dose of prednisone (25 mg/day tapered within 10 days) was also prescribed.

Laboratory exam follow-ups showed complete normalization of the white blood cell count and neutrophils after 30 days.

Discussion

Allopurinol is a structural isomer of hypoxanthine and inhibits xanthine oxidase [3]. Xanthine oxidase causes hypoxanthine and xanthine oxidation resulting in uric acid production, the result of human purine metabolism. Inhibiting xanthine oxidase reduces uric acid production and causes increases in hypoxanthine and xanthine, which are converted to closely-related purine ribotides adenosines and guanosine monophosphates. Increased levels of these ribotides block amidophosphoribosyl transferase, the first and rate-limiting enzyme of purine biosynthesis, through feedback inhibition. Allopurinol decreases both uric acid formation and purine synthesis. Though allopurinol is primarily used to treat hyperuricemia and its complications, such as chronic gout, it also treats hyperuricemia due to chronic diuretic therapy, chronic kidney disease, kidney stones, uric acid nephropathy, and protozoal infections (i.e., leishmaniasis). The drug is also indicated as an adjuvant in patients with myeloproliferative disorders or patients with elevations in serum and urinary uric acid levels while undergoing cancer therapy [4,5].

While side effects of allopurinol are rare, they are severe when they do occur. Early clinical studies using allopurinol suggested that these adverse reactions occur at an incidence rate greater than 1%. Acute attacks of gout following the

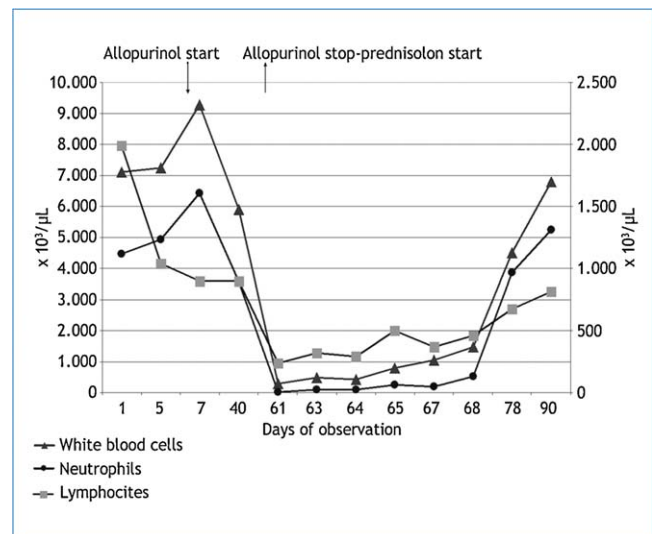


Figure 1 Chronological sequence of blood count measures during hospitalization. Arrows indicate start and stop date of drugs.

initiation of therapy were the most frequent events observed. A more recent utilization analysis suggested that the incidence of these adverse reactions is now less than 1% [4,5].

The most serious adverse effects of allopurinol are hypersensitivity syndromes consisting of fever, skin rash, eosinophilia, hepatitis, and worsened renal function, specifically Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis [4,5].

Gastrointestinal adverse events, including diarrhea, nausea, and increases in alkaline phosphatase and transaminases, are among the most frequently described reactions [4,5].

Hematologic side effects include bone marrow suppression resulting in severe anemia, thrombocytopenia, and leukopenia, which have been reported in 0.2-0.6% of patients. Studies have also described cases of aplastic anemia, agranulocytosis, eosinophilic fibrohistiocytic bone marrow lesions, pancytopenia, prothrombin decreases, anemia, hemolytic anemia, reticulocytosis, lymphadenopathy, and lymphocytosis [4–10].

Several cases of aplastic anemia have been reported leading to some fatalities [11] particularly in patients concomitantly using drugs causing bone marrow suppression and/or renal insufficiency [9,12].

Bone marrow suppression has been reported in patients treated with allopurinol [13]. Most cases occurred in patients concomitantly using bone marrow-suppressing drugs; the majority of cases occurred as early as 6 weeks and as long as 6 years after the initiation of allopurinol treatment [14].

In patients treated with allopurinol alone, cases of bone marrow suppression affecting more than one cell line have rarely been reported [4,5]. A case of acute pure red cell aplasia was reported, in a 15-year-old patient, 6 weeks after initiation of allopurinol 200 mg/day; the anemia immediately improved after discontinuation of allopurinol [15]. In another case, a 43-year-old female with chronic kidney disease

developed fever, generalized morbilliform rash, leukocytosis with marked eosinophilia, and hepatic dysfunction 3 weeks after starting allopurinol therapy (300 mg/day for 3 days followed by 200 mg/day) for hyperuricemia and arthritis. She was treated with prednisolone 15 mg/day and recombinant human erythropoietin, and eleven days later her hemoglobin level and reticulocyte counts began to increase [16].

In clinical trials, eosinophilia and leukocytosis have been reported in fewer than 1% of patients treated with allopurinol [4,5,7–10]. A macular skin rash appears to precede this hematologic adverse effect [6,17–20] and occurs in patients with underlying cirrhosis [17], diabetes mellitus [6], or concomitantly using a statin [21], azathioprine or mercaptopurine.

The outcome is often fatal, although cases with less severe neutropenia have been reversed [20,21].

In addition, a 71-year old female with concomitant hypertension and diabetes mellitus developing agranulocytosis due to allopurinol has been described in the literature; in this case, the patient died, even after immediate discontinuation of allopurinol and treatment with high steroid doses [21].

The case of an 89-year-old man with agranulocytosis, who received allopurinol along with concomitant cardiovascular therapy, has been reported. After cessation of all drugs, as well as isolation and antibiotic therapy, the leukocyte count returned to normal. However, the patient died four weeks later from progressive renal failure [22].

Recently a 43-year-old man receiving allopurinol while undergoing peritoneal dialysis was reported to have developed drug-induced agranulocytosis, as confirmed by bone marrow biopsy. After ceasing all drugs, isolating the patient, and administering a Granulocyte Colony-Stimulating Factor (G-CSF), the leukocyte count returned to normal [23].

The *Italian Pharmacovigilance Network* (Rete Nazionale di Farmacovigilanza) (RNF), reported 44 allopurinol-induced adverse reactions of the hematological system; all cases were judged as severe, and 11 events were agranulocytosis [24]. In comparison, in the *English Pharmacovigilance Network of MHRA (Medicines and Healthcare Products Regulatory Agency)*, 8 cases of agranulocytosis associated with allopurinol therapy have been reported [25].

The case report describes the development of agranulocytosis in a patient about 60 days after starting allopurinol therapy and the rapid improvement of hematological values following allopurinol discontinuation, suggesting a relationship between allopurinol and agranulocytosis. Applying the algorithm of Naranjo et al. [26], the relationship between allopurinol and the onset of agranulocytosis is classified as "possible" (score +4).

Moreover, the patient's other drugs were unlikely to cause agranulocytosis, thus indicating strong causality between allopurinol and resulting agranulocytosis. Specifically, thrombocytopenia associated with furosemide is very rare; only a few cases of leukopenia, agranulocytosis, aplastic or hemolytic anemia have been published. Also aspirin-induced aplastic anemia agranulocytosis, disseminated intravascular coagulation, purpura, eosinophilia, or pancytopenia has been only rarely described [1,2,27]. In fact, the patient had been receiving furosemide and aspirin for several years; moreover,

both drugs had been restarted upon hospital discharge without the recurrence of agranulocytosis during the follow-up period.

The mechanism for marrow suppression, and particularly allopurinol-induced agranulocytosis, is not known. The rare, unrelated and unpredictably severe adverse effects seem to indicate an idiosyncratic relationship with allopurinol or one of its metabolites.

Potential inhibition of purine and pyrimidine biosynthesis in genetically-predisposed patients could be responsible for the suppression of the marrow cell line [1,2,12,17,18,20,21].

Conclusions

This report describes a case of severe agranulocytosis associated with allopurinol therapy. Even if rarely occurring, this adverse effect could have important clinical complications. Physicians prescribing allopurinol should be aware of this side effect and strongly consider monitoring blood counts during the initial treatment period, especially in patients using multiple bone marrow suppressants and those subject to chronic renal failure [28].

Conflict of interest statement

The authors have no conflicts of interest.

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