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Case Report

Severe agranulocytosis during prolonged trimethoprim-sulfamethoxazole therapy in an elderly male: a case report with causality assessment and literature review

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ABSTRACT

Idiosyncratic drug-induced agranulocytosis (IDIA) is a rare but potentially life-threatening adverse drug reaction, most frequently associated with antithyroid drugs, clozapine, and certain antimicrobials. Trimethoprim–sulfamethoxazole (TMP–SMX), commonly prescribed for urinary tract infections (UTIs), carries a documented risk of agranulocytosis, particularly in elderly patients. We describe an 84-year-old male admitted for post-critical illness rehabilitation who developed severe febrile agranulocytosis during prolonged TMP–SMX therapy for UTI. Due to a documentation error following physician rotation, TMP–SMX (80/400 mg, two tablets every 12 hours) was administered for 31 days. On hospital day 24, he developed fever (39.4 °C), diffuse erythematous rash, leukocytes 1.2×10^9/l, absolute neutrophils 0.01×10^9/l, lymphocytes 0.52×10^9/l, and CRP 112 mg/l. TMP–SMX was discontinued and replaced by ciprofloxacin, later cefuroxime, while the patient was transferred to an infectious diseases unit where filgrastim (G-CSF) was initiated, resulting in normalization of leukocytes (7.6×10^9/l) and neutrophils (4.46×10^9/l) within seven days. Causality assessment using the Naranjo algorithm yielded a score of 7, consistent with a probable association. This case underscores the importance of accurate antibiotic stop-dates, baseline and periodic complete blood count monitoring during prolonged TMP-SMX therapy, and prompt recognition and management of febrile agranulocytosis in elderly patients.

Keywords: Trimethoprim–sulfamethoxazole, Agranulocytosis, Idiosyncratic neutropenia, Elderly, G-CSF, Causality assessment

INTRODUCTION

Idiosyncratic drug-induced agranulocytosis (IDIA), defined by an absolute neutrophil count (ANC) $<0.5\times10^9$/L, is a rare but clinically significant adverse drug reaction.[1-3] with anIts incidence of 1.6–9.2 cases per million annually in Europe. Despite improved outcomes due to early recognition and granulocyte colony-stimulating factor (G-CSF) therapy, IDIA remains associated with high morbidity and mortality, particularly in elderly or immunocompromised patients.[2,3]

Trimethoprim–sulfamethoxazole (TMP–SMX), a widely used fixed-dose antimicrobial combination, has been associated with serious hematological toxicities, including agranulocytosis.[4]

Advanced age, renal impairment, folate deficiency, prolonged therapy, and polypharmacy are recognized risk factors [4,5].5,6 We present a case of severe febrile agranulocytosis during prolonged TMP–SMX therapy in an elderly male, provide a causality assessment using the Naranjo algorithm, and discuss preventive strategies.

CASE REPORT

An 84-year-old Caucasian male was admitted on 28 March 2024 to a rehabilitation hospital following critical illness polyneuromyopathy manifesting as tetraparesis. Past medical history included cholangitis with gallbladder perforation, treated with abscess drainage and laparoscopic cholecystectomy. There were no known drug allergies. Comorbidities included benign prostatic hyperplasia, functional incontinence, and impaired mobility requiring family assistance in most activities of daily living.

Baseline examination

On admission, he was afebrile, cognitively intact, and motivated for rehabilitation. Cardiopulmonary examination revealed a systolic murmur; abdominal scars were clean without signs of infection. Neurological examination demonstrated diffuse muscle atrophy, decreased proximal muscle strength, brisk biceps reflexes, and absent lower limb reflexes. No sensory deficits were detected.

Initiation of antimicrobial therapy

Upon admission, the patient complained of dysuria. Urinalysis and Sanford test were performed, and empirical TMP–SMX (Primotren 80/400 mg, two tablets every 12 h) was initiated for suspected UTI. Culture later confirmed susceptibility to TMP–SMX. Despite symptomatic improvement within days, therapy continued for a total of 31 days due to a documentation error after physician rotation.

Clinical deterioration

On hospital day 24, the patient developed fever (39.4 °C), diffuse erythematous rash, and malaise. Laboratory results: leukocytes 1.2×10^9/l, absolute neutrophils 0.01×10^9/l, lymphocytes 0.52×10^9/l, and CRP 112 mg/l. A summary of relevant laboratory results, including hematological and inflammatory markers, is provided in Table 1.

The temporal sequence of TMP–SMX therapy, onset of febrile neutropenia, and recovery following discontinuation is illustrated in Figure 1. TMP–SMX was immediately discontinued, and ciprofloxacin was initiated, later switched to cefuroxime. Blood and urine cultures were obtained.

Transfer and management

On hospital day 25, he was transferred to an infectious diseases unit due to febrile neutropenia and persistent pyuria. Filgrastim (G-CSF) therapy was initiated, resulting in normalization of leukocyte and neutrophil counts within seven days (leukocytes 7.6×10^9/l, neutrophils 4.46×10^9/l, CRP 28 mg/l at discharge). Functional status returned to pre-event baseline.

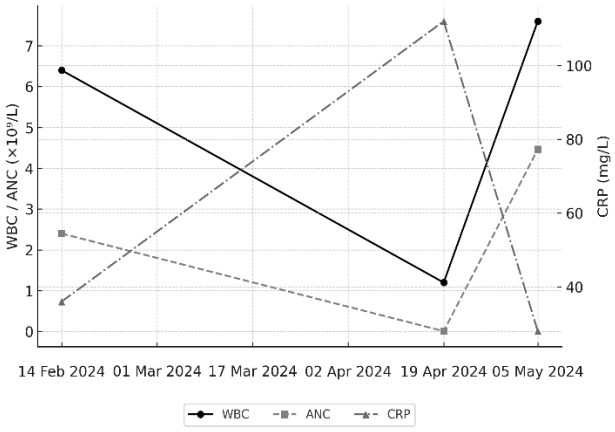

Figure 1: Timeline of clinical events, including TMP–SMX initiation, onset of fever and rash, agranulocytosis diagnosis, discontinuation of TMP–SMX, and recovery following G-CSF therapy.

Concomitant medications

During TMP–SMX therapy, the patient also received finasteride, macrogol, a plant extract supplement, dalteparin, oral nutritional supplementation, and amino acids. None of these agents are independently associated with agranulocytosis.

Causality assessment

Using the Naranjo algorithm, a total score of 7 was calculated.[6,7] Previous conclusive reports (+1), Temporal association with TMP–SMX (+2), improvement after withdrawal (+1), alternative causes excluded (+2), objective confirmation (+1), this indicates a probable relationship between TMP–SMX and agranulocytosis.

Table 1: Timeline of events, laboratory parameters, and interventions. Key laboratory results demonstrating severe neutropenia on day 24, gradual improvement after TMP–SMX discontinuation, and normalization following G-CSF therapy.

Parameter	Reference range	Day 24	Day 25	Day 32 (discharge)
Leukocytes ($\times10^9$/l)	4.0–10.0	1.2	1.4	7.6
Neutrophils ($\times10^9$/l)	2.0–7.0	0.01	0.02	4.46
Lymphocytes ($\times10^9$/l)	1.0–3.5	0.52	0.60	1.59
CRP (mg/l)	<5	112	98	28
Body temperature (°C)	< 37.5	39.4	38.7	36.9

DISCUSSION

Drug-induced agranulocytosis is a rare but potentially fatal adverse event, particularly in elderly patients due to reduced renal clearance, age-related pharmacokinetic changes, and increased polypharmacy.[2,3] TMP–SMX is a recognized trigger, with onset usually within 1–4 weeks, consistent with the 24-day latency observed here.[3-5] Proposed mechanisms include immune-mediated destruction via TMP–SMX-dependent anti-neutrophil antibodies. Direct bone marrow toxicity through reactive metabolites or folate antagonism. Prompt drug discontinuation, early recognition of febrile neutropenia, and empiric antimicrobial coverage are critical for survival.[6] G-CSF therapy accelerates neutrophil recovery and reduces hospitalization duration, as demonstrated in this case and supported by Cochrane prospective data.[9]

Preventability

This adverse event was potentially preventable. Recommended strategies include clear documentation of antibiotic stop-dates. and adherence to national formulary recommendations regarding monitoring are essential.[10] Baseline and periodic complete blood count monitoring during extended TMP–SMX therapy. Ensuring continuity of prescribing oversight during physician rotations.

CONCLUSION

TMP–SMX can cause severe idiosyncratic agranulocytosis, particularly during prolonged therapy in elderly patients. Accurate documentation, regular laboratory monitoring, and early intervention are essential to reduce morbidity and mortality.

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REFERENCES

1. Hoffman R, Benz EJ, Silberstein LE, Heslop H, Weitz J, Salama ME. Hematology E-book: basic principles and practice. Elsevier Health Sciences. 2022.
2. Andrès E, Mourot-Cottet R, Maloisel F, Séverac F, Keller O, Vogel T, et al. Idiosyncratic drug-induced neutropenia and agranulocytosis. QJM. 2017;110(5):299-305.
3. Andersohn F, Konzen C, Garbe E. Systematic review: agranulocytosis induced by nonchemotherapy drugs. Ann Intern Med. 2007;146(9):657-65.
4. Masters PA, O'Bryan TA, Zurlo J, Miller DQ, Joshi N. Trimethoprim-sulfamethoxazole revisited. Arch Intern Med. 2003;163(4):402-10.
5. Ibáñez L, Vidal X, Ballarín E, Laporte JR. Population-based drug-induced agranulocytosis. Arch Intern Med. 2005;165(8):869-74.
6. Klastersky J, de Naurois J, Rolston K, Rapoport B, Maschmeyer G, Aapro M, et al. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. Ann Oncol. 2016;27(5):111-8.
7. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45.
8. Curtis BR. Drug-induced immune neutropenia/agranulocytosis. Immunohematology. 2014;30(2):95-101.
9. Ibáñez L, Sabaté M, Ballarín E, Puig R, Vidal X, Laporte JR, et al. Use of granulocyte colony-stimulating factor (G-CSF) and outcome in patients with non-chemotherapy agranulocytosis. Pharmacoepidemiol Drug Saf. 2008;17(3):224-8.

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