Annals of Hematology & Oncology

Open Access

Austin Publishing Group

Case Report

Bactrim Induced Severe Neutropenia in an Immunocompetent Individual

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Received: June 22, 2024

Accepted: July 04, 2024

Published: July 11, 2024

Abstract

Trimethoprim-Sulfamethoxazole (TMP-SMX), also known as cotrimoxazole or Bactrim is an antimicrobial that is well tolerated and used in various clinical scenarios. One of its rarer adverse effects such as agranulocytosis is usually seen in immunocompromised individuals but can also be seen in immunocompetent individuals as seen in this case report. Non chemotherapy Idiosyncratic Drug-Induced Neutropenia (IDIN) is a rare complication associated with various drug groups which can potentially be lethal. The term neutropenia is used when Absolute Neutrophil Count (ANC) is 1.5×10^9 cells/L or less, severe neutropenia when ANC is less than 0.5×10^9cells/L, and agranulocytosis when ANC is less than 0.1×10^9cells/L. This is a case about a healthy female who developed severe neutropenia one week after trimethoprim-sulfamethoxazole use who recovered without any intervention.

Keywords: Trimethoprim-sulfamethoxazole induced severe neutropenia; Immunocompetent individual; Drug induced severe neutropenia; Antibiotic side effect

Case Report

A 27-year-old healthy female was referred to the Emergency Room (ER) for hypotension. She presented with diffuse macular rash, myalgia, widespread skin itchiness, fevers, and chills for 5 days. She recently completed Bactrim for a Urinary Tract Infection (UTI) and subsequently developed her symptoms. She reported no significant past medical or surgical history and no family history of blood or autoimmune disorders. She used to drink 1 glass of wine 4 -5 days/ week and occasionally smoked marijuana, and no other drug use. She reported allergy to penicillin and was on contraceptive pills. In the ER, her blood pressure was 91/67 mmHg, with other vitals unremarkable. On physical examination, she had a generalized papular rash on the trunk (back, chest, abdomen, thighs), sparing the upper and lower extremities. Lymph nodes were not felt on palpation of the neck. Labs showed AST- 147 U/L, ALT-72 U/L, WBC-0.8 x 10^3 cells/µL, ANC-0.3 x 10^3 cells/µL, LDH- 655 U/L, haptoglobin-318 mg/dL, GGT- 18 U/L, reticulocyte count- 0.4%. Autoimmune workup was negative for ANA, Rheumatoid factor. Infectious workup was negative for COVID, influenza A & B, EBV DNA by RT-PCR, and Parvovirus B19 DNA by PCR, HIV Ag/ Ab, Hepatitis B and C and no growth on blood cultures and urine cultures. Vitamin B 12, folic acid, iron panel were within normal limits. Peripheral blood smear showed normal RBCs and platelets, few small lymphocytes and neutrophils with cytotoxic granules. Ultrasound abdomen showed fatty liver without hepatosplenomegaly. In the hospital, she received diphenhydramine 25 mg BID with improvement in symptoms. She had a CBC 28 hours later, WBC-3.8 x 10^3 cells/µL, ANC-1.0 x 10^3 cells/µl and she was discharged with outpatient follow up. After one week, she was seen at a community Hematology clinic, labs showed

Table 1: Lab results of the patient.

	Day 1 - 10/21/23 12:38 am	Day 1 - 10/21/23 2:02 am	Day 2 - 10/22/23 6:00 am	Day 13 - 11/2/23 4:21 pm
Hemoglobin (g/dL)	10.3	11.4	10.6	11.2
Platelet (K/cmm)	127	143	165	475
WBC (K/cmm)	0.8	0.8	3.8	7.3
Absolute Neutrophil (K/cmm)	0.3	0.2	1.0	4.1
AST (U/L)	147	155	105	--
ALT (U/L)	72	86	83	--
ALP (U/L)	32	37	31	--

Citation: Kavuri S, Ramos AC, Ayaz S, Gaddam M, Iqbal R, et al. Bactrim Induced Severe Neutropenia in an Immunocompetent Individual. Ann Hematol Onco 2024; 11(3): 1456.

Table 2: Comparing different cases of TMP-SMX induced severe neutropenia in individuals.

	Case 1 [11]	Case 2 [12]	Case 3 [13]	This case report
Age/ Sex	40/ Male	53/ Male	30/ Female	27/ Female
Comorbidities	pyelolithotomy 4 weeks prior	none	--	none
WBC count	0.7 x 10^3 cells/µL	0.6 × 10^3 cells/µL	0.5 x 10^3 cells/µL	0.8 x 10^3 cells/µL
ANC count	0.0 x 10^3 cells/µL	0.0 x 10^3 cells/µL	0.22 x 10^3 cells/µL	0.3 x 10^3 cells/µL
Clinical manifestations	fever, fatigue, diffuse maculopapular rash, desquamation on extremities, oral candidiasis	Fever – 102.7 F	Pruritic rash, fevers	diffuse macular rash, myalgia, itching, fevers, chills
Drug used	TMP-SMX	TMP-SMX	TMP-SMX, doxycycline	TMP-SMX
Diagnosis/ Imaging/ Procedure	BM biopsy- hypocellularity of all cell lines	BM biopsy- no cause for agranulocytosis or concern for malignancy	LP- lymphocyte predominance, negative cultures, MRI brain- findings concerning for meningoencephalitis	--
Interventions/ Treatment	Prednisolone, antibiotics (cefepime, meropenem), transfusions: red cell concentrates, thrombocyte, whole blood, filgrastim	None/ observation	Antibiotics (cefepime, vancomycin), filgrastim, dexamethasone, IV acyclovir	None/ observation
Outcome	Death	Agranulocytosis resolution after drug discontinuation	Symptom resolution	Symptom resolution

Symbols and Abbreviations: TMP-SMX: Trimethoprim-Sulfamethoxazole; WBC: White Blood Cell; ANC: Absolute Neutrophil Count; BM: Bone Marrow; LP: Lumbar Puncture; MRI: Magnetic Resonance Imaging.

an improvement WBC-7.3 x 10^3 cells/µL, ANC-4.1 x 10^3 cells/µL. She did not receive any antibiotics or Granulocyte Colony-Stimulating Factor (G-CSF) and her symptoms resolved.

Discussion

Neutropenia can be caused by intrinsic or extrinsic factors. Intrinsic causes include metabolic disorders, autoimmune conditions, myelodysplastic syndromes, leukemias, congenital neutropenia, hypersplenism, etc. Extrinsic causes include chemotherapy, drug induced, vitamin deficiency, sepsis, alcohol use, etc. [3]. Drug induced neutropenia is due to either decreased neutrophil production or increased clearance. Decreased production due to bone marrow suppression is seen with chemotherapeutic agents, while increased clearance is attributed to drug induced autoantibody destruction.

Non chemotherapy drugs can be associated with IDIN, a life-threatening complication of some non-chemotherapeutic drugs. Although rare, it has an incidence of 2.4 to 15.4 million cases and a mortality of ~ 5%. Increased mortality is seen in those with age > 65 years, comorbidities such as renal disorders, and sepsis [3]. According to a study conducted by the Berlin Case-Control Surveillance Study (FAKOS), 63 of the 88 patients with agranulocytosis were identified to have drug related agranulocytosis [4].

Many mechanisms have been proposed to explain IDIN, with hapten (drug) induced antibody production most frequently suggested [1, 3, 5]. The drug gets oxidized to a hapten and gets bound to a protein to form a hapten-protein complex, leading to antibody production. Antibodies form against neutrophil glycoprotein drug complexes leading to their destruction [3]. The drugs most frequently associated with IDIN include propylthiouracil, methimazole, amoxicillin, spironolactone, clozapine, trimethoprim- sulfamethoxazole, valganciclovir, amoxicillin, etc. [1-6].

Patients with agranulocytosis can manifest with varying degrees of severity. Symptoms can range from asymptomatic, to sepsis and possibly death. A cohort study reviewed data from 203 patients diagnosed with IDIN and reported common clinical manifestations to be isolated fever (26.3%), septicemia (13.9%), sore throat and acute tonsillitis (9.3%), pneumonia (13.4%), and septic shock (6.7%) [2]. In this case report, the patient presented with a generalized rash, myalgias, and fevers.

Diagnosis is made via detailed history, clinical examination, and lab results or by detecting neutrophil drug dependent antibodies (DDAbs) using enzyme linked immunosorbent assay (ELISA), flow cytometry, monoclonal antibody immobilization of granulocyte antigens, immunoblotting, granulocytotoxicity, or granulocyte agglutination. Testing through these methods is rarely used due to their complexity and lack of availability [1, 3]. In this case report, the patient was diagnosed with severe neutropenia through detailed history and an ANC of 0.3 x 10^3 cells/µL.

First line of treatment includes discontinuation of the offending agent. Most cases show an improvement in neutrophil count with drug discontinuation. Some patients require symptomatic treatment with antihistamines for itching and rash, or treatment/ prophylactic antibiotics. The average duration for neutrophil recovery is 9 days (range of 9-24 days). Patients at high risk, those with multiple comorbidities, age >65, severe infection, ANC of less than 0.1 x 10^9 cells/ L, and a prolonged course of neutropenia may benefit from hematopoietic growth factors such as granulocyte-colony stimulating factor (G-CSF). In some case reports, G-CSF is shown to shorten duration of neutrophilia (P= 0.015), antibiotic course, hospital stay, and lower risk of complications [3, 5, 7]. Patients with ANC equal to or greater than 0.1 x 10^9 cells/L had fewer complications when compared to those with ANC of less than 0.1 x 10^9 cells/ L [5].

TMP-SMX is a combination of two antibiotics that act in the same pathway to prevent the formation of tetrahydrofolate (THF) which plays a major role in bacterial DNA synthesis [8]. It is cost-effective and used in common illnesses such as UTIs, pyelonephritis, toxoplasmosis, Pneumocystis jirovecii /Pneumocystis Carinii Pneumonia (PJP/PCP), etc. Common adverse effects include rash, urticaria, photosensitivity, nausea, vomiting, fatigue, insomnia, or tinnitus. More life-threatening reactions include Stevens-Johnson syndrome, agranulocytosis, renal failure, myelosuppression, pancreatitis, hepatotoxicity, and anemias [9]. A study in Sweden reported 154 cases of blood dyscra-

sias attributed to TMP-SMX use. Blood dyscrasias ranged from affecting one cell line to multiple lines. There were 61 cases of leukopenia with 16 cases of agranulocytosis, 32 cases of bicytopenia and 31 cases of tricytopenia. The overall fatality rate was 17%, with a higher fatality seen in those with tricytopenias. In general, the incidence of TMP-SMX related hematological adverse effects was low in relation to the prescription sales [10]. Asymptomatic patients or patients with less severe symptoms may go unnoticed but more attention should be given to the life-threatening adverse effects when starting a patient on TMP-SMX and they should be closely monitored for immediate interventions.

Few case reports have been published in which Bactrim was found to have caused severe neutropenia. One case resulted in death while the other 2 cases resulted in symptom resolution upon discontinuing the drug. One case is of a 40-year-old male with a history of pyelolithotomy who was prescribed Bactrim for post operative fever. He presented with fever, fatigue, diffuse rash and oral candidiasis, a WBC count of 0.7 x 10^3 cells/µL, and ANC of 0.2 x 10^3 cells/µL. He was given antibiotics, steroids and transfused red cell concentrates, thrombocyte, and whole blood, and filgrastim. Bone marrow showed hypocellularity of all cell lines, and severely depressed WBC. Patient was transferred to a specialty hospital for continuation of treatment but eventually died despite all efforts [11]. Another case is a 53-year-old male who presented with a fever of 102.7 F after completing Bactrim for cellulitis. Labs showed WBC of 0.6 × 10^3 cells/µL and ANC of 0.0 x 10^3 cells/µL, and bone marrow biopsy was unremarkable. Neutropenia resolved without any treatment, and WBC improved to 8.9 × 10^3 cells/µL and ANC of 4.1 x 10^3 cells/µL [12]. Another case is of a 30-year-old female who was prescribed doxycycline and Bactrim pre and post operative for abdominoplasty and mammoplasty. She presented with rash and fevers, and her WBC was 0.5 x 10^3 cells/µL, with ANC of 0.22 x 10^3 cells/µL. She was given IV antibiotics and filgrastim but eventually developed meningoencephalitis. She was then given dexamethasone and acyclovir, with eventual resolution of her rash, fevers and other symptoms [13].

Conclusion

IDIN is one of the rarer and life-threatening adverse effects of TMP-SMX. Although most cases have resolution of symptoms and recovery of neutrophil count without any interventions, some cases need close monitoring, antibiotics, and filgrastim. High risk patients have an increased risk of mortality and require intervention irrespective of symptoms. Although it is a rare adverse effect of TMP-SMX, it is even rarer to see a healthy patient develop severe neutropenia due to TMP-SMX. Patients on TMP-SMX must be closely monitored for such complications for earlier interventions.

Symbols and Abbreviations: Trimethoprim-Sulfamethoxazole (TMP-SMX), White blood cell (WBC), Absolute Neutrophil Count (ANC), Bone Marrow (BM), Lumbar Puncture (LP), Magnetic Resonance Imaging (MRI).

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