CASE REPORT

Successful Management of Antithyroid Drug-Induced Agranulocytosis Using Granulocyte Colony-Stimulating Factor: A Case Report

Nur Arfah Rizki[1], Hendra Zufry[2,3,4], Krishna W Sucipto[2,3,4], Agustia Sukri Ekadamayanti[2,3,4]

1 Residency Program in Internal Medicine, Department of Internal Medicine, Faculty of Medicine, Universitas Syiah Kuala
2 Division of Endocrinology, Metabolism, and Diabetes-Thyroid Center, Department of Internal Medicine, Faculty of Medicine, Universitas Syiah Kuala
3 Division of Endocrinology, Metabolism, and Diabetes-Thyroid Center, Dr. Zainoel Abidin Hospital
4 Innovation and Research Center of Endocrinology, Faculty of Medicine, Universitas Syiah Kuala

*Corresponding author:
Hendra Zufry, MD.
Division of Endocrinology, Metabolism, and Diabetes-Thyroid Center, Department of Internal Medicine, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia
Email: hendra_zufry@usk.ac.id

ABSTRACT

Agranulocytosis is a rare condition and occurs in all age groups. Incidence ranges from 6 to 8 cases per million population per year. About 70% of the cases are found to be involved with medication usage. The use of granulocyte colony-stimulating factor (G-CSF) is effective for antithyroid drug (ATD)-induced agranulocytosis, though some patients do not respond. A 22-year-old female was diagnosed with Grave's disease (GD) three months ago and began using Methimazole (MMI) at an initial dose of 20 mg/day. She was taken to the emergency room after complaining of a fever and stomachache for a week. Laboratories: The patient had leucopenia (white blood cell count 2040/mm3) and severe neutropenia, with an absolute neutrophil count (ANC) of 122.4/μL, thyroid stimulating hormone (TSH) of 0.005 IU/mL, and free thyroxine (FT4) of 46.81 pmol/L. The patient received G-CSF, which normalized her neutrophil counts after the first injection and resolved her fever. She was recommended to quit methimazole therapy. MMI is thionamide used as a first-line treatment for GD. The most severe side effect is agranulocytosis. Agranulocytosis can have various presentations; it most frequently occurs between 2 weeks and 3 months after the initiation of treatment. If the patient recovers, granulocytes begin to reappear in the periphery within a few days to 3 weeks. This drug-induced agranulocytosis is a lethal condition but reversible if recognized early and treated accordingly. G-CSF may shorten the recovery period.

Keywords: Agranulocytosis, grave's disease, antithyroid drug, granulocyte colony-stimulating factor

INTRODUCTION

Agranulocytosis occurs when the absolute neutrophil count (ANC) is fewer than 100 neutrophils per microliter of blood. It is possible to inherit or acquire agranulocytosis. Agranulocytosis is a hazardous illness that can have lethal effects. To prevent mortality from septicemia, early detection and treatment are necessary.[1] The reported incidence of agranulocytosis, a rare disorder that affects people of all ages, ranges from 6 to 8 instances per million population annually. Medication use is shown to be linked in almost 70% of the instances. It also happens more often in women than in men, possibly because women use medications more often or because autoimmune illnesses are more common in women. Agranulocytosis is not racially biased.[2]

The early symptoms include malaise, fever, and chills, or infections that commonly occur in the form of ulcers, necrotizing lesions of the gingiva, the floor of the mouth, buccal mucosa, throat, or other locations within the oral cavity.[1] When clinicians encounter patients with agranulocytosis, the first response is typically to employ granulocyte colony-stimulating factor (G-CSF) as an emergency intervention; G-CSF is beneficial for (antithyroid drug) ATD-induced agranulocytosis, while some patients do not respond.[3]

Hematopoietic growth factors stimulate neutrophil production, maturation, migration, and cytotoxicity. Agents used to treat agranulocytosis include filgrastim, a granulocyte colony-stimulating factor (G-CSF), sargramostim, a granulocyte-macrophage colony-stimulating factor, and pegfilgrastim (a long-acting filgrastim).[1] Over the last 20 years, granulocyte colony-stimulating factors (G-CSFs) have been the main therapeutic choice for treating patients with neutropenia.[4] Malcolm Moore and Karl Welte discovered granulocyte colony-stimulating factor (G-CSF) from human cells in 1984. It was the foundation for filgrastim, one of the most important cancer treatments. In the hierarchical development of hematopoiesis, G-CSF primarily drives the myeloid cell series from committed progenitor cells to mature neutrophil granulocytes.[5]

CASE ILLUSTRATION

A 22-year-old female was admitted to the Emergency Room complaining of fever and abdominal pain for a week. Fever complaints all day long, a febrifuge reduces fever. She also complains of nausea, vomiting three or more times each day, and decrease in appetite so that could only complete half of a plate of regular meals, but not accompanied by weight loss. There are no complaints of urination and defecation. Patient with ongoing fatigue, palpitations, and tremors since three months ago. Previously, she was diagnosed with Grave's Disease the last three months ago and started Methimazole at an initial dose of 20 mg/day and a beta-blocker for symptom control.

Were Upon first admission, the vital sign BP 152/96 mmHg, HR: 128 bpm regular, RR 22 tpm, T 38,5^{o}C, On physical examination we found exophthalmos and a diffuse enlargement of the thyroid gland. Examination of the abdomen found tenderness in the epigastric. On the thorax, we found a dilated. The left heart border was obtained, Left boundary of the heart in Intercostalis V was 2 cm from linea midclavicularis sinistra. Laboratories found (table 1) leucopenia (white blood cell count 2040/mm^3) and severe Neutropenia, absolute neutrophil count (ANC) 122,4/µL with multinational association of supportive care in cancer (MASCC) score 24 (low risk) clinical index of stable febrile neutropenia (CISNE) score 3 or high risk. Differential counting showed: 6% neutrophils, 81% lymphocytes, 9% monocytes, 3% eosinophils, and 1% basophils. Thyroid stimulating hormone (TSH): 0.005 ulU/mL and free thyroxine (FT4) 46.81 pmol/L, confirmed the diagnosis of hyperthyroid.

This patient was diagnosed with ATD-induced agranulocytosis and impending thyroid stom (Burch wartofsky score: 40). Because of serious concern about ATD, she was advised to discontinue methimazole treatment promptly. A granulocyte colony-stimulating factor and

antibiotics were provided after a week. The WBC and granulocyte counts were evaluated 3 days during hospitalization.

Table 1. Laboratory Examination of Patient in Day 1,3, and 6

Inspection	Day 1st	Day 3rd	Day 6th	Normal Range
Hemoglobin	10,0	9,8	9,9	14,0 - 17,0
Hematocrit	29	29	30	45 - 55
Erythrocytes	4,0	3,9	3,9	4,7 - 6,1
Thrombocytes	330	381	454	150 - 450
Leukocytes	2,04	2,01	12,75	4,5 - 10,5
MCV	73	74	78	80 - 100
MCH	25	25	25	27 - 31
MCHC	35	33	33	32 - 36
Eosinophils	3	0	0	0 - 6
Basophils	1	2	1	0 - 2
Stem Neutrophils	0	0	0	2 - 6
Segmented Neutrophils	6	50	80	50 -70
Lymphocytes	81	39	13	20 - 40
Monocytes	9	9	6	2 - 8
FT4	46,81			9 - 20
TSHs	0,005			0,25 - 5
ANC	122,4	1.005	10.200	1.500 – 8.000

Three Days after the injection of GCSF, it was found that ANC started to increase by 1.005 /µL, Day 6th after the third injection 10.200/µL. We decided to stop injecting G-CSF. The methimazole treatment was terminated on admission due to concern for drug-induced agranulocytosis. Subsequently, her infectious workup was negative and antibiotics were stopped. The patient received granulocyte stimulating colony factor with normalization of her neutrophil counts and resolution of her fever.

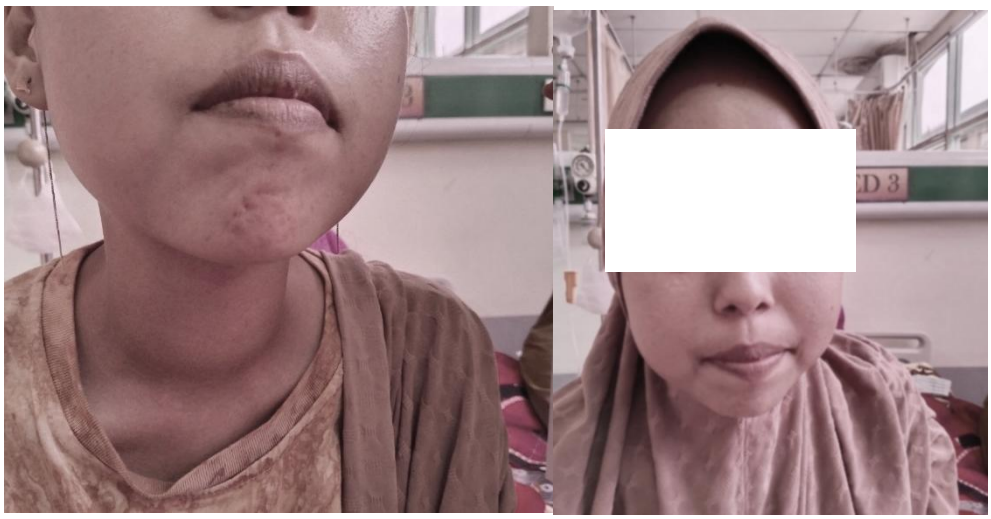

Figure 1. Clinical picture of the patient showed diffuse thyroid enlargement and exophthalmos

DISCUSSION

Methimazole (MMI) is a thionamide used as the first-line therapy for Graves' disease (GD). MMI has mild adverse effects such as skin rash and liver problems, with agranulocytosis being the most serious. Agranulocytosis often appears within 2-3 months of starting medication. Treatment with thioamide propylthiouracil (PTU) is more likely to cause serious adverse effects such as hepatotoxicity, vasculitis, and polyarthritis compared to MMI.[6]

Agranulocytosis can cause a variety of symptoms, including fever, chills, and sore throat. It can be a life-threatening illness that demands immediate diagnosis and treatment.[1] Agranulocytosis is a potentially fatal side effect of antithyroid drug (ATD) treatment. Its incidence is 0.2% to 0.5%, and its mechanism is unknown. Antithyroid drugs are commonly used to control hyperthyroidism, especially when patients refuse other therapies such as radioiodine and surgery. Despite their acceptability, especially in Eastern countries, antithyroid drugs are associated with many complications. Of the known complications, antithyroid drug-induced agranulocytosis, although rare, is the most severe and life-threatening.[7]

Agranulocytosis can be roughly categorized into two types: hereditary and acquired. The hereditary condition is caused by genetic abnormalities in the gene that codes for neutrophil elastase, or ELA2. The most prevalent alterations are intronic substitutions, which deactivate a splicing site in intron 4. Diseases can be acquired as a result of numerous drugs, toxins, autoimmune problems, or infections.[8]

The following are the medications commonly involved with agranulocytosis:[9]

1. Cancer chemotherapies
2. Analgesic and anti-inflammatory (gold, naproxen, and penicillamine)
3. Anti-thyroid (carbimazole, propylthiouracil)
4. Anti-arrhythmics (quinidine, procainamide)
5. Anti-hypertensives (captopril, enalapril, nifedipine)
6. Antidepressants/psychotropics (clozapine, amitriptyline, dosulepin, mianserin)
7. antimalarials (pyrimethamine, dapsone, sulfadoxine, chloroquine)
8. Anticonvulsants (phenytoin, sodium valproate, carbamazepine)
9. Antibiotics (sulphonamides, penicillin, cephalosporins)
10. Miscellaneous (cimetidine, ranitidine, chlorpropamide, zidovudine)

Infections that can cause agranulocytosis include:

1. Bacterial (typhoid fever, shigella enteritis, brucellosis, tularemia, tuberculosis)
2. Rickettsial (rickettsialpox, human granulocytic anaplasmosis, Rocky Mountain spotted fever)
3. Parasitic (kala-azar, malaria)
4. Viral (human immune deficiency, Epstein-Barr virus, cytomegalovirus, hepatitis viruses, human herpesvirus

Agranulocytosis is thought to occur according to the following mechanisms:

1. when the drug attaches to the granulocyte, antibody production begins to destroy granulocytes;
2. antibodies may target the drug metabolites complex absorbed on the neutrophil granulocyte in the presence of plasma component; and
3. the drug may cause the production of autoantibodies.[10]

If agranulocytosis is identified, the medication should be stopped, the patient should be watched for infection symptoms, and antibiotics should be started if needed. Factors that stimulate granulocyte colonies may reduce the healing time. Within a few days to three weeks, granulocytes start to return to the periphery if the patient recovers; a normal granulocyte count soon follows.[10] It has been observed that G-CSF treatment of ATD-induced agranulocytosis reduces the mortality rate from 21.5 to 5%.[11] Infection is the primary agranulocytosis consequence. The frequency of infection is closely correlated with the length and intensity of agranulocytosis. The incidence of infection reaches 100% when the ANC stays below 100 cells per microliter of blood for more than three to four weeks.[1]

Another serious side effect of agranulocytosis is sepsis. The clinical state known as sepsis is brought on by the body's dysregulated reaction to an infection. Sepsis, bacteremia, and septic shock result from the body's inability to combat the offending pathogens due to a significant reduction in the number of mature granulocytes caused by agranulocytosis. A distributive or vasodilatory shock that causes circulatory and metabolic problems and is linked to a greater death risk is septic shock.[1]

Since agranulocytosis is a dangerous illness, therapy should be started right once. Regardless of whether the patient exhibits symptoms or not, any suspected offending drugs or agents should be stopped as soon as agranulocytosis is confirmed. It normally goes away one to three weeks after the offending agent is ceased if it is caused by drugs or another substance. In the meanwhile, general care measures like gargles, anesthetic gel for oral and gingival lesion discomfort, and good oral hygiene to avoid infection of the teeth and mucosa are beneficial. Constipation can be treated with stool softeners. Abrasions and skin infections need to be treated right away.[1]

Before and after the introduction of G-CSF, the beginning patterns of agranulocytosis caused by antithyroid drugs were divided into the following two categories: The asymptomatic group had no signs or symptoms of infection throughout the disease, while the symptomatic group had signs and symptoms of infection as the initial clinical features of agranulocytosis or, when agranulocytosis was identified by routine WBC count monitoring, symptoms were absent and infection only developed a few days later despite stopping antithyroid medication therapy. G-CSF has been used to treat all individuals with agranulocytosis brought on by antithyroid medications since July 1990. Until the granulocyte count exceeded 109/L, a subcutaneous dosage of 75 g G-CSF was given every day. Bone marrow punctures were sometimes done once at the development of agranulocytosis or granulocytopenia and again during the recuperation phase.[12]

G-CSF is the mainstay of therapy since it dramatically speeds up granulopoiesis regeneration. Due to higher rates of bacterial resistance, G-CSF prophylaxis is suggested by the ASCO recommendations as a better way to avoid infections than antibiotic prophylaxis. G-CSF promotes neutrophil regeneration following allogeneic stem cell transplantation. Increased rates of both acute and chronic graft-versus-host disease (GvHD) have been reported in certain investigations. Meta-analyses, however, revealed a one-day advantage in neutrophil regeneration but no discernible rise in the risk of GvHD. Hospital stay duration and survival were unaffected.[5]

CONCLUSION

Agranulocytosis occurs generally within a few weeks or months of taking the anti-thyroid medication but onset may be delayed by one year. This drug-induced agranulocytosis is a lethal condition but reversible if recognized early and treated accordingly. In patients with ATD-induced agranulocytosis, the recovery duration can be substantially reduced by G-CSF.

ACKNOWLEDGMENTS

We would like to extend our sincere gratitude to the Department of Internal Medicine and the staff of the Emergency Room at RSUDZA, for their invaluable support during the diagnosis and management of this case. We are also grateful to the laboratory team for their meticulous attention to patient monitoring and laboratory analysis, which greatly contributed to the successful management of this case. Lastly, our thanks to our colleagues and mentors for their constant encouragement and guidance.

REFERENCES

1. Sedhai YR, Lamichhane A, Gupta V. Agranulocytosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2025 Jul 3].
2. García G.C, Navarro E, Alcázar V, López-Guzmán A, Arrieta F, Anda E, et al. Therapeutic management and long-term outcome of hyperthyroidism in patients

with antithyroid-induced agranulocytosis: A retrospective, multicenter study. J Clin Med. 2023;12(20):6556.
3. MacKay M, Clewis MC, Sweet P. Antithyroid drug-induced agranulocytosis: A case report. Cureus. 2023;15(11):e48038.
4. Theyab A, Alsharif KF, Alzahrani KJ, Oyouni AAA, Hawsawi YM, Algahtani M, et al. New insight into strategies used to develop long-acting G-CSF biologics for neutropenia therapy. Front Oncol. 2023;12:1026377.
5. Link H. Current state and future opportunities in granulocyte colony-stimulating factor (G-CSF). Support Care Cancer. 2022;30(9):7067-77.
6. Yoshimura Y, Matsushima K, Goshima Y, Hoshino Y, Nakashima S, Inaba T, et al. A case of methimazole-induced acute pancreatitis with an HLA allele causing antithyroid drug-induced agranulocytosis. J Endocr Soc. 2022;6(5):bvac038.
7. Malboosbaf R, Azizi F. Long-term treatment with antithyroid drugs: Efficacy and safety. Int J Endocrinol Metab. 2020;18(Suppl).
8. Andrès E, Federici L, Weitten T, Vogel T, Alt M. Recognition and management of drug-induced blood cytopenias: the example of drug-induced acute neutropenia and agranulocytosis. Expert Opin Drug Saf. 2008;7(4):481-9.
9. Vicente N, Cardoso L, Barros L, Carrilho F. Antithyroid drug-induced agranulocytosis: State of the art on diagnosis and management. Drugs R D. 2017;17:91-6.
10. Mariya A, Sreenath R, Maria D. A case report of carbimazole induced agranulocytosis. Indian J Pharm Pract. 2023;16(3):152-4.
11. El-Shareif HJ. Agranulocytosis: A rare complication of the thioamides. Egypt J Intern Med. 2023;35(1):59.
12. Tajiri J, Noguchi S. Antithyroid drug-induced agranulocytosis: how has granulocyte colony-stimulating factor changed therapy? Thyroid. 2005;15(3):292-7.