

Antithyroid Drug-Induced Agranulocytosis: Management Challenges: Experience from 10 Cases

Mohammad Fariduddin¹, Marufa Mustari², Tania Tofail^{3*}, Shahjada Selim⁴, Tahniyah Haq⁴, Sharmin Jahan⁴, Murshed Ahamed Khan⁴, Nusrat Sultana⁴, Hurjahan Banu², Fatima Begum⁵ and Muhammad Abul Hasanat⁵

¹Professor and Chairman, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh

²Fellow, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh

³Resident, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh

⁴Assistant Professor, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh

⁵Professor, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh

*Corresponding Author: Tania Tofail, Resident, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh.

Received: April 23, 2020; Published: July 06, 2020

Abstract

Aim: To share our experience of Antithyroid drug (ATD)-induced agranulocytosis. Agranulocytosis is a well-recognized fatal complication of ATD.

Methods: We managed ten patients of ATD induced agranulocytosis and we used standardized case record form to collect data.

Results: Of the 10 cases the dose of Carbimazol used were 30 to 80 mg/day (mean \pm SD: 43.75 \pm 5.81 mg/day) for 10 to 84 days. The absolute neutrophil counts were $< 500/\text{mm}^3$ in 7 and < 1000 in all cases. The age ranged from 20 to 68 years and female 75%. Clinically all (100%) cases had fever and sore throat. Bleeding gum and epistaxis in 3 cases and sepsis and shock were present in 3 cases. Carbimazol was stopped in all cases; of which 2 were inadvertently switched to PTU but developed agranulocytosis again. All cases recovered following withdrawal of drugs and supportive management. Radio-ablation was done in all cases. Initially one case was managed with lugol's iodine therapy and another one with plasmapheresis. Rests were managed with lithium. It took two to three weeks for response (50% of baseline FT4 level) with 800 - 1000 mg lithium/day.

Conclusion: Patients given ATD must report for "fever and sore throat". Lithium is effective to control hyperthyroidism prior to radio-ablation in patients of agranulocytosis.

Keywords: Agranulocytosis; Antithyroid Drugs; Hyperthyroidism; Lithium; Radioablation

Introduction

Antithyroid drugs (ATD) are one option for treatment of hyperthyroidism, along with radioactive iodine and surgery. Except in North America where radioactive iodine is preferred as the treatment ATD are used nearly everywhere else, including Bangladesh. The most serious adverse effect of ATD, which may lead to fatal complications, is agranulocytosis. Its incidence was reported to be less than 1% and the estimated risk was 3 per 10,000 patients per year [1]. In this study, we report on a 10 patients with ATD-induced agranulocytosis from July 2013 to August 2018.

Methods

Patients who developed agranulocytosis as a result of thionamide/propylthiouracil formed the basis of the study. A standardized case record form was used to record demographic data, thyroid disease, concomitant medical illness, dosage and duration of antithyroid drugs. Clinical presentations, treatment, duration of recovery of leucocyte count after discontinuing medication and final outcome of patients with agranulocytosis induced by antithyroid drugs were also recorded in the form.

Statistical analysis was performed by SPSS software version 24.0. Results with descriptive variable were expressed as mean \pm SD. and two sub-groups on Absolute Neutrophil Count (ANC) with $< 500/\text{mm}^3$ in 7 and $> 500/\text{mm}^3$ in 3 were compared with t test for groups.

Results

Primary etiology of hyperthyroidism was Graves's Disease (GD) in nine and multi-nodular goiter (MNG) in one case. Of the 10 cases the dose of Carbimazol used were 30 to 80 mg/day (mean \pm SD: 43.75 ± 5.81 mg/day) for 10 to 84 days (mean \pm SD: 36.9 ± 6.7 days). The absolute neutrophil counts were (ANC) $< 500/\text{mm}^3$ in 7 (70%) cases and $< 1000/\text{mm}^3$ in all cases. The age range was 20 to 68 years (mean \pm SD: 40.6 ± 5.23 years) and had a female preponderance; female: male = 4:1. Clinical manifestations of all (100%) cases were fever and sore throat; but bleeding gum and epistaxis, sepsis and shock were present in 3 cases. Carbimazol was stopped in all cases; of which 2 were inadvertently switched to PTU but developed same complication (prior to referral). All cases recovered following withdrawal of drugs. GM-CSF was not used to hasten recovery of ANC. All cases received radio-ablation as definitive therapy. Before radio-ablation one case was managed with lugol's iodine therapy and plasmapheresis was used in another one. Rests were managed with lithium. On an average, it took two to three weeks for response (50% of baseline FT_4 level) with lithium and dose required was up to 800 - 1000 mg/day. After conservative management, all the patients recovered. Radio-ablation was given as the definitive treatment to all cases. One case relapsed following receiving radio ablation and others were euthyroid. The relapsed one has been treated with radio ablation with a higher dose.

According to absolute granulocyte count (AGC) there were two subsets of populations i) 7 (5 female and 2 males) with AGC $< 500/\text{cc}$ and ii) 3 (all females) with AGC $> 500/\text{cc}$. Group comparison study documented the population with AGC $< 500/\text{cc}$ is older: as mean (+ SE) $43.29 (+ 6.83)$ vs $34.33(+ 7.45)$ years; p .185; were exposed to a higher dose of carbimazole $43.57 (+ 6.70)$ vs $35.00 (+ 5.00)$ mg/day; p .459 and for longer duration $41.00 (+ 8.79)$ vs $26.00 (+ 9.85)$ days; p .349). None of the differences are not statistically significant.

Discussion

Agranulocytosis is a well-recognized fatal complication of ATD use during management of Hyperthyroidism/Thyrotoxicosis. Its incidence is not common. In one of the largest series, it (an absolute granulocyte count of less than 500 per cubic millimeter) was found in 0.37% and 0.35% of patients who were receiving propylthiouracil and methimazole respectively [2].

The transient, mild granulocytopenia (a granulocyte count of less than 1500 per cubic millimeter) do not fall in this group. The cause list of such condition include i) Graves' disease, ii) some ethnic population such African decadents or iii) patient on ATDs. It is wise to have a baseline differential white-cell count before initiation of ATD. That will help to differentiate ATD induce transient mild granulocytopenia from other causes. There are reports of cases of agranulocytosis occurring during subsequent use ATD in relapse of hyperthyroidism how had no such complication during initial course(s) of treatment.(I,III-V) One cases of our series (case no 10) with Grave's Disease had such a history.

In majority cases, ATD-induced agranulocytosis occurs within 2 months of treatment [1,5-7].

In our study, the onset of agranulocytosis was between 10 to 84 days (mean \pm SD: 36.9 ± 6.7 days) after treatment with ATD. Some study documented age is an independent risk of mortality from agranulocytosis [3]. The relative risk of developing agranulocytosis in patients over age 40 was 6.4 times than the younger patients (p < 0.001) [8]. In our series, age (as mean \pm SD) is 38.5 ± 4.32 years (See table 1).

Drug dose is also an another risk for agranulocytosis. In one series, 8.6-fold increased risk of agranulocytosis was documented for cases with more than 40 mg/day of Carbimazol than the less than 40 mg/day ($p < 0.01$) [8]. In our series, dose of Carbimazol used is 30 to 80 mg/day (mean \pm SD: 43.75 ± 5.81 mg/day) (See table 1).

Case no.	Age	Sex	Primary diagnosis	Drug	Max. dose (mg/day)	Duration (days)	Symptom
1	26	M	GD	CBZ	80	45	1 and 2
1				PTU	150	30	1 and 2
2	55	F	GD	CBZ	30	10	1 and 2
3	38	F	GD	CBZ	30	45	1 and 2
4	53	M	GD	CBZ	30	42	1 and 2
5	45	F	MNG	CBZ	30	12	1, 2 and 4
6	28	F	GD	CBZ	45	40	1, 2 and 6
7	21	F	GD	CBZ	45	84	1, 2 and 5
7				PTU	150	3	1 and 2
8	50	F	GD	CBZ	45	45	1, 2 and 3
9	20	F	GD	CBZ	45	21	1, 2 and 3
10	49	F	GD	CBZ	30	21	1, 2 and 3

Table 1: Data table of 12 episodes of agranulocytosis in 10 cases.

N.B: Sex: M: Male and F: Female; Primary diagnosis: GD: Graves’s Disease and MNG: Multinodular Toxic Goiter. Drug: CBZ: Carbimazole and PTU: Propylthiouracil. Symptoms: 1: Fever; 2: Sore Throat; 3: Rash; 4: Bleeding (Gum bleeding and, epistaxis); 5: Sepsis and 6: Shock. In our series, dose of Carbimazol used is 30 to 80 mg/day (mean \pm SD: 43.75 ± 5.81 mg/day).

All cases were treated with withdrawal of CBZ plus symptomatic support. Case no 1 and 7 were given 150 gm of PTU per and relapse occur in both cases.

We used fever and sore throat in patient on ATD as the clinical clue for screening for agranulocytosis. Therefore, these were present in all our cases. But literature shows these features are most common presentation of agranulocytosis patients [5]. Other feature we documented are epistaxis, bleeding, sepsis and shock. Incidence of them were in 30% of cases. The absolute neutrophil counts were (ANC) $< 500/\text{mm}^3$ in 7 (70%) of our cases and $< 1000/\text{mm}^3$ in all cases (See figure 1).

Out of 10 cases we have used Lithium carbonate in 7 patients to control hyperthyroid features prior to radio ablation. The starting dose was 400 mg SR formulation. Later the dose was increased to 800 - 1000 mg. Around 3 weeks’ time (range 10 - 30 days) were required for response (50% of baseline FT_4 level). Serum lithium concentration was monitored by obtaining 12 hour post dose sample. Lithium is concentrated by the thyroid gland at a level 3 to 4 times of that in the plasma, probably by active transport [7]. The primary mechanism of lithium is the inhibition of thyroid hormone release by inhibiting the action of TSH on cAMP. Lithium may also inhibit thyroid hormone synthesis [7,9-11]. Responses to lithium treatment may vary (See table 2).

In one patient who was 8 weeks pregnant at the time of initial diagnosis, later developed agranulocytosis and neutropenic sepsis lithium could not be used as an alternative therapy. During her pregnancy she was managed with lugol’s iodine. After 28 weeks of her pregnancy she was advised thyroidectomy for control of her symptoms but she refused. Following delivery she was unfortunately prescribed propylthiouracil and again developed the same complication. Thereafter she was stopped PTU and managed conservatively. Following

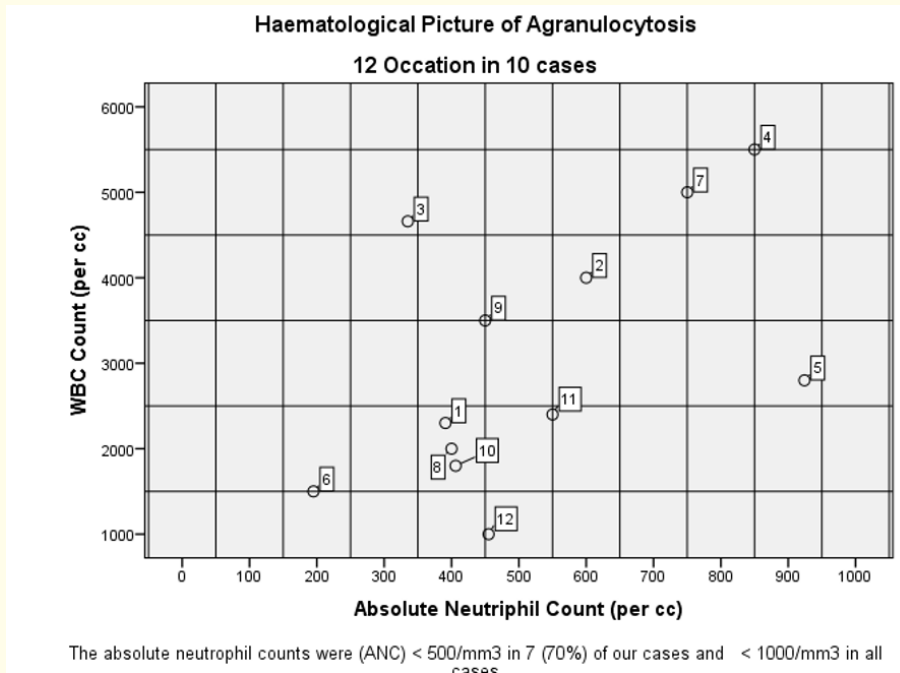


Figure 1: Haematological feature of agranulocytosis.

Case no.	Age	Diagnosis	Offender drug	ANC	WBC Count	Treatment to control	Definite Treatment
1	26	GD	CBZ	335	4660		
1			PTU	391	2300	Lithium	RAI
2	55	GD	CBZ	1540	5500	Lugols Iodine	RAI
3	38	GD	CBZ	924	2800	Lithium	RAI
4	53	GD	CBZ	195	1500	Lithium	RAI
5	45	MNG	CBZ	1750	5000	Lithium	RAI
6	28	GD	CBZ	400	2000	Lithium	RAI
7	21	GD	CBZ	450	3500		
7			PTU	1600	4000	Lithium	RAI
8	50	GD	CBZ	406	1800	Lugol's Iodine	RAI
9	20	GD	CBZ	750	2400	Lithium	RAI
10	49	GD	CBZ	800	1000	Plasmapheresis	RAI

Table 2: Data table of treatment of 12 episodes of agranulocytosis in 10 cases.

The absolute neutrophil counts were (ANC) < 500/mm³ in 7 (70%) of our cases and < 1000/mm³ in all cases.

Out of 10 cases we have used Lithium carbonate in 7 patients to control hyperthyroid features prior to radio ablation. The starting dose was 400 mg SR formulation. Later the dose was increased to 800-1000 mg. Around 3 weeks' time (range 10 - 30 days) were required for response (50% of baseline FT₄ level).

improvement, lithium was given to control hyperthyroidism followed by radioablation. The major actions of iodide on thyroid function are inhibition of thyroid hormone release from the thyroid gland and a transient decrease in thyroid hormone synthesis (the acute Wolff-Chaikoff effect) [7].

TPE is a useful adjunct in the treatment of hyperthyroidism; its use is suggested in cases with severe thyrotoxicosis with cardiac or neurological complications, or when standard antithyroid treatments are either unresponsive or contraindicated.

The American society of apheresis categorizes the use of TPE in the treatment of hyperthyroidism as category III which states that the role of TPE has not been established in the treatment of thyroid storm [12]. TPE is an extracorporeal blood purification technique used to for eliminating large molecular substances from the plasma [13]. In a patient with impending thyroid storm we applied plasmapheresis to render the patient euthyroid rapidly prior to radio ablation and found very good response. Only a single session could bring down FT₄ level from 4.18 ng/dl to 2.08 ng/dl.

Radio-ablation was given as the definitive treatment to all cases. One case relapsed following receiving radio ablation and others were euthyroid. The relapsed one have been treated with radio ablation with a higher dose (15 mi curie).

Conclusion

All cases on ATD (CBZ/PTU) having fever and sore throat should undergo CBC examination to identify agranulocytosis. Withdrawal of ATD and supportive symptomatic treatment are effective. Control of hyperthyroidism by lithium therapy prior to radio-ablation is an effective choice when thionamides cannot be used. Outcome of agranulocytosis is better now a days with early recognition and effective interventions.

Bibliography

1. Cooper DS. "Antithyroid Drugs". *The New England Journal of Medicine* 352.9 (2005): 905-917.
2. Tajiri J and Noguchi S. "Antithyroid Drug-Induced Agranulocytosis: Special Reference to Normal White Blood Cell Count Agranulocytosis". *Thyroid* 14.6 (2004): 459-462.
3. Pearce SHS. "Spontaneous reporting of adverse reactions to carbimazole and propylthiouracil in the UK". *Clinical Endocrinology (Oxford)* 61.5 (2004): 589-594.
4. Weetman AP. "Graves' Disease". *The New England Journal of Medicine* 343.17 (2000): 1236-1248.
5. Li KL, et al. "Agranulocytosis associated with anti-thyroid drug in patients with Graves' thyrotoxicosis--report of 11 cases". *Changcheng Yi Xue Za Zhi* 14.3 (1991): 168-173.
6. Sheng WH, et al. "Antithyroid-drug-induced agranulocytosis complicated by life-threatening infections". *QJM - Monthly Journal of the Association of Physicians* 92.8 (1999): 455-461.
7. DS Cooper. "Treatment of thyrotoxicosis". In Werner and Ingbar's the Thyroid a Fundamental and Clinical Text, L. E. Braverman and D. S. Cooper, Editions (2013): 492-516,
8. Cooper DS, et al. "Agranulocytosis associated with antithyroid drugs. Effects of patient age and drug dose". *Annals of Internal Medicine* 98.1 (1983): 26-29.
9. Mori M, et al. "Inhibitory Effect of Lithium on the Release of Thyroid Hormones from Thyrotropin-Stimulated Mouse Thyroids in a Perifusion System". *Endocrinology* 124.3 (1989): 1365-1369.

10. Williams JA, et al. "Thyroid Secretion *in Vitro*: Inhibition of TSH and Dibutyryl Cyclic-AMP Stimulated ¹³¹I Release by Li + 1". *Endocrinology* 88.6 (1971): 1385-1388.
11. Spaulding SW, et al. "The Inhibitory Effect of Lithium on Thyroid Hormone Release in Both Euthyroid and Thyrotoxic Patients". *The Journal of Clinical Endocrinology and Metabolism* 35.6 (1972): 905-911.
12. Schwartz J, et al. "Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue". *Journal of Clinical Apheresis* 31.3 (2016): 149-162.
13. Jha S, et al. "Thyroid Storm Due to Inappropriate Administration of a Compounded Thyroid Hormone Preparation Successfully Treated with Plasmapheresis". *Thyroid* 22.12 (2012): 1283-1286.

Volume 3 Issue 8 August 2020

©All rights reserved by Tania Tofail, et al.