Successful Treatment with Radioiodine for Antithyroid Drug-Induced Agranulocytosis in Graves' Disease

[1]Jasmin Ferdous, [2]Fatima Begum, [3]Papia Akhter, [3]Shamsun Nahar Bailey, [4]Zeenat Jabin

[1]Associate Professor & PMO, National Institute of Nuclear Medicine & Allied Sciences (NINMAS), Block-D, BSMMU Campus, Shahbag, Dhaka-1000

[2]Professor & Head, Thyroid Division, NINMAS

[3]Assistant Professor & SMO, NINMAS

[4]Director & Chief Medical Officer, INMAS, ShSMCH campus

Correspondence Address: Dr. Jasmin Ferdous. Associate Professor & PMO, NINMAS, Block-D, BSMMU Campus, Dhaka
Email: jasmin.ferdous.aelee@gmail.com

ABSTRACT

Background: Graves' disease (GD) is an autoimmune disorder and the leading cause of hyperthyroidism. Antithyroid drugs (ATDs) are available treatment option. Agranulocytosis is a rare but potentially fatal complication of ATD in hyperthyroidism management. The study's objectives include clinical symptoms of ATD-induced agranulocytosis in Graves' illness and the difficulties in clinical care in addition to radioactive iodine therapy (RAIT).

Methods: Twelve patients with ATD induced agranulocytosis referred to NINMAS between 2021to 2022 for RAIT therapy were included in this study. All the patients with hyperthyroidism and agranulocytosis or leukopenia were taken in this study.

Results: The age of the 12 patients (female: male = 10:3) was 26 to 56 years (mean SD: 38.41±13.9 years). Among the twelve patients 10 were treated with carbimazole and two with PTU for Graves' disease. Initial dose of ATD was 15-30 mg daily. The most common clinical manifestations were fever (100%), sore throat (41.6%), oral ulcer (16%), rash (41.66%), loose motion (16.66%) and atrial fibrillation (8.33%) with deep vein thrombosis (DVT). Agranulocytosis developed between 7th and 547th days after initiation of ATD; all of them developed early onset except one who developed agranulocytosis after 1.5 years of initiation of ATD. All 12 patients were treated immediately after diagnosis of agranulocytosis following prompt discontinuation of ATD, they were treated with antibiotic with 12 cases, G CSF in one case, KI in one case, glucocorticoid in two cases, and beta blocker in all cases. After intensive and supportive treatment in hospital, all the patients recovered with absolute neutrophil counts of more than 500/mm3 in 5 to 15 days (mean SD: 7.6 3.4 days). Nine patients were treated with lithium carbonate supplement to reduce FT3 level. Average dose of lithium carbonate was 600 mg. After that patients were referred for RAIT. TRAb were positive in seven patients and average were 4.2 U/L. Plasmapheresis was done in three patients and one patient in two times due to high FT4 level before RAIT. Lithium carbonate supplementation reduce thyroid hormone level but not to the optimum level. All the 12 patients were treated with RAIT. Average dose RAI 10.9 mCi, average follow up period 2.3 years. Two patients required second dose of RAIT due to persistent hyperthyroidism. Six patients became hypothyroid, two were in hyperthyroid state (on plan for second therapy), four patients are euthyroid at present and they are on follow up. No fatal condition was found in this study.

Conclusion: The most cost-effective method of managing agranulocytosis induced by thionamide-derived ATD is that all patients with thyrotoxicosis must be informed that their white blood cells and differential counts should be checked immediately whenever the "common cold" symptoms occur during treatment, especially within the first three months of medication. Contraindication to ATDs; RAI is a safe and effective alternative.

Keywords: Graves' disease, Agranulocytosis, Lithium, radioactive iodine therapy.

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INTRODUCTION

Graves' disease (GD) is an autoimmune disease that is the most common cause of hyperthyroidism. GD predominantly affects women between the 2nd and 4th decades of life (1). The leading cause of autoimmune hypersecretion of thyroid hormone from the thyroid gland is circulating thyrotropin (TSH) receptor antibodies (2). Thionamide-derived antithyroid drugs (ATDs) (Carbimazole, Methimazole, and Propylthiouracil), radioiodine (RAI), and surgery are available treatments for GD (3). Some known toxic effects of ATDs include fever, rash, pruritus, hepatocellular injury, and agranulocytosis (3). The presence of granulocytes <500/mm^3 following ATDs is defined as "ATD-induced agranulocytosis" (4). ATDs-induced toxic reactions can be seen in 3–12% of the patients (5). ATD-induced agranulocytosis is a rare but potentially life-threatening condition. In this situation, the use of thionamide-containing drugs is contraindicated, and RAI

or surgery are the therapeutic alternatives (6). However, alternative drugs for patients who are intolerant of or unresponsive to thionamides are limited. Iodide compounds can be effective but will interfere with the subsequent uptake of radioiodine. Perchlorate and thiocyanate are often not sufficiently compelling. Their serious side effects, like irreversible aplastic anemia and methemoglobinemia, have reduced their acceptance. The use of lithium to treat thyrotoxicosis was reported in the 1970s as it affects thyroid hormone release and synthesis (7). It is a common drug for the treatment of bipolar disorders. The experience with lithium is much more extensive than with perchlorate or thiocyanate. Although lithium has a narrow therapeutic index, it appears safe if serum levels are closely monitored. The objectives of the study are to describe the clinical manifestations of ATD-induced agranulocytosis in GD and the challenges faced in clinical management along with radioactive iodine therapy (RAIT).

METHODS

Twelve patients with ATD-induced agranulocytosis who were referred to NINMAS between 2021 and 2022 for RAIT therapy were included in this study. All the patients with hyperthyroidism, agranulocytosis, or leukopenia were selected for this study. As soon as agranulocytosis was diagnosed, ATD was discontinued. After blood samples were taken for bacterial culture, all patients were treated with parenteral antibiotics. One patient was administered subcutaneous granulocyte-colony stimulating factor (G-CSF), 300 g per day, for two days. White blood cells and differential counts were checked every day in the first week and then every two days to see the treatment response. After recovery, all patients with ATD-induced agranulocytosis were followed up and referred to us for RAIT. The results were presented as the mean $\pm$ standard deviation.

RESULTS

In NINMAS, 510 patients received RAIT for hyperthyroidism in 2021-2022, with 12 developing ATD-induced agranulocytosis (2.35%). The age of the 12 patients (female: male = 10:3) was 26–56 years (mean SD: 38.58 + 13.9 years). Among the twelve patients, 10 were treated with carbimazole and two with PTU for Graves' disease. The initial dose of ATD was 15–30 mg daily. The characteristics of these patients are summarized in Table 1. The most common clinical manifestations were fever (100%), sore throat (41.6%), oral ulcer (16%), rash (41.66%), loose motion (16.66%), and atrial fibrillation (8.33%) with deep vein thrombosis (DVT). Agranulocytosis developed between the 7th and 547th days after initiation of ATD; all of them developed early onset except one, who developed agranulocytosis after 1.5 years of initiation of ATD. All 12 patients were treated immediately after diagnosis of agranulocytosis following prompt discontinuation of ATD; they were treated with antibiotics in 12 cases, G-CSF in one case, KI in one case, glucocorticoids in two cases, and beta blockers in all cases. After intensive and supportive treatment in the hospital, all the patients recovered with absolute neutrophil counts of more than 500/mm^3 in 5 to 15 days (7.6 $\pm$ 3.4 days). Nine patients were treated with a lithium carbonate supplement to reduce their FT3 level. The average dose of lithium carbonate was 600 mg per day. Their average blood lithium levels were 0.45 mmol/L. After that, patients were referred for RAIT. Average FT3 (7.3 pg/ml), FT4 (30.62 pmol/L), and TSH (.01 mIU/L) levels prior to therapy. TRAb was found to be positive in seven patients, with an average level of 4.2 U/L. Plasmapheresis was performed on three patients, with one patient receiving it twice due to high FT4 levels prior to RAIT. Lithium supplementation reduces thyroid hormone levels, but not to the optimal level. All 12 patients were treated with RAIT. The average RAI dose was 10.9 mCi, and the average follow-up period was 2.3 years. Two patients required a second dose of RAIT due to persistent hyperthyroidism. Their FT4 level was >33 pmol/L. Six patients became hypothyroid; two were in a hyperthyroid state (on plan for second therapy); four are euthyroid at present, and they are on follow-up. This study found no comorbidity and no fatal condition.

Table-1: Clinical details of the Graves' disease patients diagnosed with antithyroid drug-induced agranulocytosis followed by radio iodine treatment.

Patient	Age/sex	Symptoms	Neutrophil Count (normal value : 40-75%)	FT3 level Pg/ml (N: 1.45-4.10)	Supportive treatment	Definitive Treatment	Outcome
1	45/female	Fever, blister, loose motion	7%	7.85	Lithium Carbonate (Sustained release) , Broadspectrum antibiotic	RAIT	Hypothyroid
2	27/female	Fever, sore throat	3.7%	4.05	Lithium Carbonate (Sustained release) , Broadspectrum antibiotic	RAIT	Hyperthyroid
3	55/female	Fever, blister, loose motion, MR, AF	3.6%	4.68	Lithium Carbonate (Sustained release) , Broadspectrum antibiotic	RAIT	Hypothyroid
4	18/female	Fever, sore throat, cough	5%	6.12	Lithium Carbonate (Sustained release) , Broadspectrum antibiotic, plasmapheresis (2 times)	RAIT	Hypothyroid
5	51/female	Fever, rash	3.5%	6.3	Lithium Carbonate (Sustained release) , Broadspectrum antibiotic	RAIT	Hypothyroid
6	57/female	Fever, sore throat	4.2%	5.3	Lithium Carbonate (Sustained release) , Broadspectrum antibiotic	RAIT	Hyperthyroid
7	40/female	Fever, rash	8%	4.6	Lithium Carbonate (Sustained release) , Broadspectrum antibiotic	RAIT	Hyperthyroid
8	23/female	Fever, rash, sore	5.3%	5.8	Lithium Carbonate (Sustained release) , Broadspectrum antibiotic	RAIT	Euthyroid
9	56/female	Fever, oral ulcer	8%	13	Lithium Carbonate (Sustained release) , Broadspectrum antibiotic	RAIT	Euthyroid
10	33/female	Fever, oral ulcer	6.5%	9.8	Lugol's Iodine, Broad spectrum antibiotic	RAIT	Euthyroid
11	32/male	Fever, sore throat	5%	10.5	Lithium Carbonate (Sustained release) , Broad spectrum antibiotic	RAIT	Euthyroid
12	26/male	Fever, rash	3%	10.7	Lithium Carbonate (Sustained release) , Broad spectrum antibiotic	RAIT	Hyperthyroid

DISCUSSION

The reported incidence of ATD-induced agranulocytosis in hyperthyroid patients is less than 1% (8). ATDs can be associated with toxic reactions in 3–12% of patients (9, 10). A total of 510 patients were treated with RAIT for hyperthyroidism in 2021–2022 at NINMAS, and among them, 12 (2.35%) developed ATD-induced agranulocytosis.

Some studies have shown that MMI is responsible for a minor side effect, while PTU causes a major severe adverse event, and agranulocytosis is more likely to occur with PTU. In this study, eleven patients developed agranulocytosis on carbimazole and one on PTU.

In most cases, agranulocytosis occurs within 90 days after initiation of ATD therapy, but this complication may occur much later (after a year or more) after medication. In this study, eleven patients developed early-onset symptoms, and one developed agranulocytosis 1.5 years later. Cooper DS et al. reported that most of the ATD-induced agranulocytosis usually occurs within two months of treatment (11, 12).

Li KL, Huang HS, et al. reported In a 10-year retrospective study, it was found that three patients with GD who did not suffer from ATD-induced agranulocytosis in the first treatment course suffered from this serious adverse event during treatment for recurrent hyperthyroidism (13). In this study, one patient developed agranulocytosis due to recurrent hyperthyroidism.

Agranulocytosis usually occurs within the first month after initiation of ATD therapy with high doses, intermittent use, and in elderly individuals. However, it

may occur regardless of treatment duration or age (14). In this study, the age of the 12 patients (female: male = 10:2) was 26–56 years (mean SD: 38.41 ±13.9 years). Among the twelve patients, ten were treated with carbimazole and two with PTU for GD. The initial dose of ATD was 15-30 mg daily.

Our observation was, high fever was the earliest symptom in 12 patients, which is similar to other published reports. Other manifestations were a sore throat (41.6%), an oral ulcer (16%), a rash (41.66%), loose motion (16.66%), and atrial fibrillation (8.33%) with deep vein thrombosis (DVT).

Management of agranulocytosis includes suspension of ATDs and antibiotics (15). In this study, all patients received antibiotics with the suspension of ATD, and one received G-CSF. G-CSF accelerates neutrophil recovery and is used when neutrophils are <500/mm^3 (16). One patient also received glucocorticoid injection. After treatment in the hospital, all the patients recovered with absolute neutrophil counts of more than 500/mm^3 in 5 to 15 days (mean SD: 7.6 ±3.4 days).

Lithium (Li) affects cell function by inhibiting ATPase, cAMP, and inositol phospholipid metabolism. In vitro, it decreases the response of cultured cells to thyrotropin-releasing hormone (TRH). The thyroid gland is capable of Li uptake and concentration. It inhibits iodine uptake through sodium-iodide symporter interference and interferes with tyrosine iodination. Li promotes the conversion of thyroxine to triiodo-thyronine in the thyroid gland (17). Lithium carbonate is usually used to treat manic-depressive and depressive disorders (18). However, lithium carbonate can also decrease the levels of thyroid hormones and lead to hypothyroidism during the treatment. So, it is also used as a second-line drug to treat hyperthyroidism. The relevance of the relationship between lithium treatment and thyroid function is well documented (19). The serum monitoring of lithium levels is essential for the safety of patients and clinical effectiveness (20). Our clinical study shows that lithium carbonate is safe and has no severe side effects in the treatment of hyperthyroidism. In this study, nine patients were treated with a lithium carbonate supplement to reduce the FT3 level. The average dose of lithium carbonate was 600 mg per day, and their blood lithium level was 0.45 mmol/L. Thyroid hormone levels are reduced by lithium supplementation, but not to the optimal level.It is also effective for the preparation of radioactive iodine. All 12 patients in this study were treated with RAIT. The average RAI dose is 10.9 mCi, with a 2.3-year follow-up period.Two patients required a second dose of RAIT due to persistent hyperthyroidism. Their FT4 level was >33 pmol/L. Six patients became hypothyroid, two are in a hyperthyroid state (on plan for second therapy), and four are euthyroid at present and are on follow-up. So, RAIT is a good treatment option for patients with complications due to the use of ATD.

From the observations of the present study, it might be emphasized that the clinical follow-up of patients using thioamides is essential. These patients should be advised on the signs and symptoms of agranulocytosis, as well as the need for suspension of medication and medical care if they present with a fever or sore throat. Management of ATD-induced agranulocytosis is puzzling, but proper management is possible with early diagnosis. In this study, no fatal condition is detected. When ATDs are absolutely contraindicated, thioamide-free regimens are required to control hyperthyroidism until definitive treatment.

CONCLUSION

Thionamide-induced agranulocytosis is a rare complication, and its consequences can be minimized with an early diagnosis. According to this study, fever and sore throat were the first and most important clinical signs of ATD-induced agranulocytosis. Alerting the patient regarding symptoms of this complication is fundamental. With a contraindication to ATDs, RAI, rather than surgery, is a safe and definitive therapeutic option in GD.

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