

## Carbimazole-induced agranulocytosis treated with propylthiouracil

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### Abstract

Antithyroid drugs may result in serious adverse events which require prompt alteration of therapy and adequate supportive measures. A 29-year-old female patient presented with a history of swelling in front of her neck for 3 months and cough, sore throat, and palpitation for 1 month. She was diagnosed as a case of Hyperthyroidism and was prescribed carbimazole 15 mg thrice daily. She was relatively well for 2 weeks with medications but after that, she experienced high-grade fever with chills and rigors associated with sore throat. Then she consulted with an Endocrinologist and was started on granulocyte colony-stimulating factor (G-CSF) with discontinuation of carbimazole. Barrier nursing and a broad-spectrum antibiotic (3<sup>rd</sup> generation cephalosporins) were used to treat her neutropenic sepsis and propylthiouracil was initiated. Her symptoms resolve following radio-iodine ablation and her thyroid function status is currently euthyroid. [*J Assoc Clin Endocrinol Diabetol Bangladesh, January 2022; 1 (1): 35-37*]

**Keywords:** Agranulocytosis, Carbimazole, Propylthiouracil, Granulocyte colony-stimulating factor

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### Introduction

The major agents for treating thyrotoxicosis are drugs of the thionamide class: carbimazole (CBZ), methimazole (MMI), and Propylthiouracil (PTU). CBZ is rapidly decarboxylated in the liver to the active substance MMI.<sup>1</sup> Antithyroid drugs (ATDs) like CBZ are typically introduced at high doses 40–60 mg daily although lower doses are reasonable in individuals with only modest elevation of T<sub>4</sub> and T<sub>3</sub>. Usually, this leads to subjective improvement within 10-14 days and clinical and biochemical euthyroidism within 6-8 weeks. At this point, the dose can be reduced and titrated to maintain T<sub>4</sub> and TSH within their reference range.<sup>2</sup> The adverse reactions to antithyroid drugs almost always occur within the first 3 months of therapy. Agranulocytosis is usually heralded by a severe sore throat and fever.<sup>3</sup> Management starts with specific antibiotic therapy to combat infections, myeloid growth factors-specifically, granulocyte colony-stimulating factors (G-CSF) and granulocyte-macrophage

colony-stimulating factors, and general care.<sup>4</sup>

### Case history

A 29-year-old female patient presented with a history of swelling in front of her neck for 3 months and cough, sore throat, palpitation, and weight loss for 1 month. She also complained of excessive menstrual bleeding for the last 3 days. She was non diabetic, normotensive, no history of asthma, cardiac or renal disease. Examination revealed – temperature: 100°F; pulse rate: 118/min, regular; blood pressure: 100/60 mm of Hg; respiratory rate: 30 cycles/min. Thyroid gland was diffusely enlarged. She was clinically thyrotoxic. Systemic examination was unremarkable. Investigations are shown in Table-I. Ultrasonogram (USG) of thyroid revealed diffusely enlarged thyroid gland and thyroid scan showed intense radiotracer concentration in the thyroid.

Finally, she was diagnosed as a case of hyperthyroidism due to Graves' disease for which Carbimazole was started 15 mg thrice daily.

**Table-I:** Investigation profile of the patient

Investigations	Initial	1 <sup>st</sup> Follow up	2 <sup>nd</sup> Follow up
Hemoglobin (g/dL)	12.8	10.2	9.2
ESR (mm in 1 <sup>st</sup> hour)	14	33	26
TC of WBC (cells/cmm)	11800	1600	28000
DC of WBC (%)	Neutrophil 70% Lymphocyte 21%	Neutrophil 2% Lymphocyte 94%	Neutrophil 82% Lymphocyte 10%
Platelet (/cmm)	450000	-	-
Creatinine (mg/dl)	0.7	-	-
ALT (U/L)	40	45	45
Bilirubin (mg/dL)	-	2.4	0.8
Random blood glucose (mmol/L)	6.7	-	-
TSH (mIU/L)	0.005	-	-
T4 (nmol/L)	359.8	-	-

ESR: Erythrocyte sedimentation rate; TC of WBC: total count of white blood cell; DC of WBC: Differential count of white blood cell; TSH: thyroid-stimulating hormone; ALT: Alanine transaminase

She was relatively well for 2 weeks after starting medications but after that she complained of high-grade fever with chills and rigors associated with sore throat. Investigations are shown in Table - I (1<sup>st</sup> Follow-up).

Carbimazole was withheld and empirical antibiotic therapy given in view of neutropenic sepsis. After assessment of liver function, PTU was started along with Inj. G-CSF for 5 days. After that investigations were repeated (Table-I, 2<sup>nd</sup> Follow up). Thyroid function test was also done and it was near the normal range. Then after a complete evaluation and proper management, radioiodine therapy was given after 16 days of PTU without any complications. After receiving radioiodine therapy she is now hypothyroid and on levothyroxine replacement 100 microgram/day.

### Discussion

Hyperthyroidism is a common endocrine disorder; incidence is 2% for women and 0.2% for men.<sup>7</sup> Anti-thyroid drugs (ATD) reduce the synthesis of new thyroid hormones by inhibiting the iodination of tyrosine.<sup>2</sup> In general, ATD as first-line therapy is most useful in young patients with small glands and mild disease. The drug is given for 1 to 2 years, and then it is tapered or discontinued to see whether the patient has achieved remission.<sup>3</sup> ATDs can have adverse effects. Agranulocytosis is a rare but potentially serious complication (0.2%–0.5%).<sup>2</sup> ATD-induced agranulocytosis is diagnosed, when there is a

well-matched clinical history, an absolute neutrophil count of  $0.5 \times 10^9/L$  or less, and bone marrow histological features consistent with agranulocytosis.<sup>6</sup> The underlying mechanisms for agranulocytosis as a cause of ATD have four different immunological reactions. First, antibodies may develop against the ATD when it is bound to the cell membrane of the granulocyte, resulting in accelerated destruction of the granulocyte. Second, antibodies may target the drug metabolite complex that has been adsorbed to the neutrophil granulocyte in the presence of plasma components. Thirdly, the drug may trigger the production of autoantibodies. Finally, the interaction of a granulocyte antigen and drug may induce the production of antibodies. PTU is commonly used for the treatment of Graves' disease. They share similar inhibitory effects on thyroid hormone biosynthesis by interfering with thyroid peroxidase (TPO) mediated oxidation and organification of iodine. The initial dose for Graves' disease can be started at 50 to 150 mg three times a day. It has been reported that 0.37% of patients using PTU and 0.35% of patients using methimazole / carbimazole have severe agranulocytosis.<sup>10</sup> Our patient has got PTU for 16 days but during that time, there were no PTU-induced adverse effects like agranulocytosis, jaundice, dark urine, light stools, abdominal pain, loss of appetite, nausea, or other evidence of liver dysfunction. The patient was clinically and biochemically euthyroid. Radio iodide<sup>131</sup> therapy is the treatment when intolerant to thioamides.<sup>3</sup>

## Conclusions

In conclusion, hyperthyroidism is a common condition treated mostly with antithyroid medications. The adverse reactions to ATDs almost usually occur within the first 3 months of therapy, especially agranulocytosis (about 0.5% of patients) which requires immediate cessation of ongoing antithyroid drug therapy, institution of appropriate antibiotic therapy, and shifting to alternative therapy.

## Acknowledgement

We are grateful to our patient for giving the consent to report the case.

## Conflict Of Interest

There are no conflicts of interest.

## Financial Disclosure

The author(s) received no specific funding for this work.

## Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

Written informed consent was obtained from the study participant. All methods were performed in accordance with the relevant guidelines and regulations.

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**How to cite this article:** Das S, Chowdhury C, Kar A, Kashem CT, Uddin MR, Mallick S, Akter F. Carbimazole-induced agranulocytosis treated with propylthiouracil. *J Assoc Clin*

*Endocrinol Diabetol Bangladesh*, 2022; 1 (1): 35-37

## Publication History

Received on: 29 October 2021

Accepted on: 23 December 2021

Published on: 1 January 2022

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