Case Report

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Turbulent voyage of a patient with Graves hyperthyroidism complicated by carbimazole-induced agranulocytosis: Challenges to induce euthyroidism

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Abstract

Carbimazole (CBZ) induced agranulocytosis is a rare but potentially life-threatening complication. The treatment of choice in this condition is definitive therapy like radioactive iodine (RAI) ablation or thyroidectomy. Prior to RAI ablation euthyroidism should be attained to lower the risk of thyroid function deterioration and treatment failure. A 19-year-old girl with Graves hyperthyroidism and a previous history of CBZ-induced agranulocytosis came for definitive management. She was treated with lithium, therapeutic plasma exchange, and cholestyramine with dexamethasone sequentially to render euthyroidism while awaiting elective RAI ablation. But none of these measures successfully normalized her thyroid function. Propylthiouracil (PTU) started with close monitoring and she became nearly euthyroid biochemically after about two weeks. RAI ablation was done after withholding PTU for five days. She became hypothyroid five months after RAI ablation and levothyroxine replacement started. This case highlights the challenges in treating hyperthyroidism prior to elective RAI ablation in a patient with CBZ-induced agranulocytosis. *[J Assoc Clin Endocrinol Diabetol Bangladesh, July 2023; 2 (2):75-78]*

Keywords: Carbimazole, Propylthiouracil, agranulocytosis, radioactive iodine ablation

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Introduction

Carbimazole (CBZ) is a widely used anti-thyroid drug that rapidly decarboxylated in the liver to the active substance methimazole. Though generally well tolerated, CBZ may rarely causes agranulocytosis defined as a granulocyte count below 0.5×10^9/L, that is often accompanied by serious infection and is a potentially life-threatening condition.[1] CBZ-induced agranulocytosis usually occurs in the early stages of therapy and it is more common in elderly patients and in those taking high doses of CBZ.[2,3] However, in such conditions, the preferred choice of treatment is definitive therapy like radioactive iodine (RAI) ablation or total thyroidectomy. Thyrotoxicosis may be worsened soon after RAI ablation due to radiation-induced leakage of stored thyroid hormone.[4] So, normal or near-normal thyroid function should be ensured to avoid the potential transient aggravation of thyrotoxicosis during or after RAI ablation.[5] There are various pharmacological and non-pharmacological approaches to treat thyrotoxicosis prior to elective RAI ablation. This case highlights various pharmacological and non-pharmacological measures' effectiveness in normalizing thyroid function when CBZ is contraindicated.

Case Summary

A 19-year-old girl presented with a diagnosed case of Graves thyrotoxicosis. She had a history of CBZ-induced agranulocytosis about 10 months back while she was taking CBZ in a dose of 20 mg tds. At that time she was hospitalized and recovered after 10 days without any other complications of neutropenia (Figure-1). Since then she was on lithium 400 mg twice daily and propranolol 20 mg tds. But euthyroidism was not achieved. She was not in regular follow-up. Two months back she got admitted to our department. She was prepared for RAI ablation but unfortunately got infected with COVID-19 and we discharged her with lithium 400 mg bd and propranolol 20 mg tds.

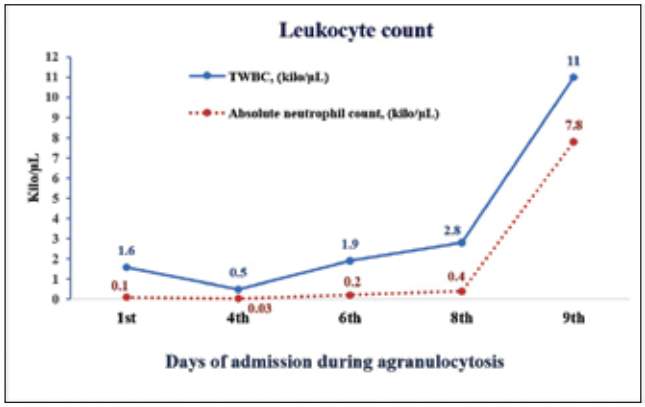

Figure-1: Total leukocyte and absolute neutrophil counts during admission with agranulocytosis

She again got admitted with severe thyrotoxicosis after recovering from COVID-19. Lithium was stopped. Then she was treated with two sessions of therapeutic plasma exchange (TPE), and cholestyramine 4 gm tds for 7 days with dexamethasone 5 mg tds intravenously sequentially to render euthyroidism while awaiting elective RAI ablation. But none of these measures successfully normalized her thyroid function (Figure-2).

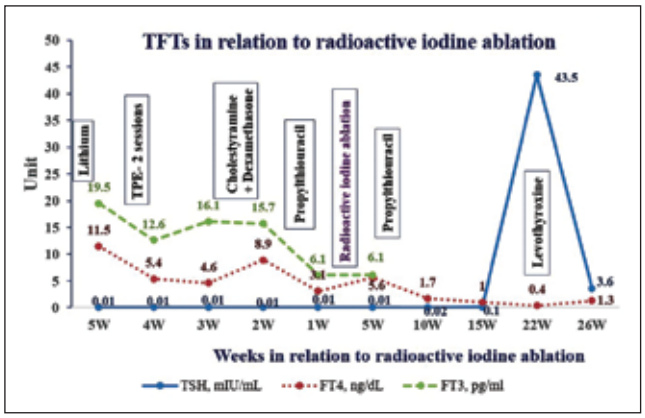

Figure-2: Changes in thyroid function tests with different antithyroid measures in relation to the radioactive iodine ablation

Propylthiouracil (PTU) started at a low dose (50 mg bd) and a gradual increment of dose with monitoring of complete blood count and thyroid function was done. She became nearly euthyroid biochemically after about two weeks with PTU 100 mg tds. Her blood count was also normal. RAI ablation was done after withholding PTU for five days. Then PTU resumed after five days and continued for four months with regular follow-up. She became hypothyroid at five months and levothyroxine replacement started. Now she is euthyroid with levothyroxine replacement (Figure-2).

Discussion

CBZ-induced agranulocytosis is a rare but potentially life-threatening complication. In such conditions, definitive therapy like RAI ablation or total thyroidectomy is the preferred choice of treatment. But, prior to RAI ablation, euthyroidism should be attained to lower the risk of thyroid function deterioration and treatment failure. Various pharmacological and non-pharmacological approaches can be used to treat thyrotoxicosis while awaiting elective RAI ablation in such conditions. A previous case series from our department also showed different approaches to achieving euthyroid status.[6]

Lithium inhibits the coupling of iodotyrosine residues thereby preventing the synthesis of thyroxine (T4) and triiodothyronine (T3) and also inhibits thyroid hormone release from the follicular cell. It can be used as an adjunct to RAI ablation as it promotes the retention of thyroid hormone in the thyroid gland.[7]

Cholestyramine, an ion exchange resin, has been shown to interfere with the absorption of ingested thyroid hormones and the enterohepatic circulation of endogenous thyroid hormones. It can be used as a short-term adjunctive agent for thyrotoxic patients in whom there is an urgent need to control the thyrotoxic state.[8]

Therapeutic plasma exchange (TPE) is a highly effective blood purification procedure whereby blood is separated via centrifugation or filtration into plasma and cells. The cells are then returned to the patient, replacing the plasma with either donor plasma, fresh frozen plasma (FFP), albumin, or a similar colloidal solution.[9] TPE can be a lifesaving procedure to obtain a transitional euthyroid state as the effect of TPE is gradual and only transient, lasting less than 3-4 days.[10]

PTU appears to be radioprotective which can be overcome by increasing the radioiodine dose. Well-documented cross-reaction between CBZ and PTU was observed regarding agranulocytosis.[11] Very little evidence was found regarding the use of PTU as an alternative therapy to CBZ-induced agranulocytosis.[12]

RAI ablation has been used for thyrotoxic patients to successfully render them euthyroid in the setting of thionamide induced agranulocytosis and may represent a safe treatment alternative for patients with a stable

clinical presentation. Patients should be on a reduced iodine diet and antithyroid medication should be stopped prior to therapy and resumed one week after RAI ablation if necessary. Lifelong follow-up is important to ensure that the recurrence of the disease or hypothyroidism can be treated.[13]

In our case, the definitive treatment of thyrotoxicosis could either be RAI ablation or thyroid surgery; however, an attempt to arrange either was unsuccessful initially. Hence, the patient was treated sequentially with lithium, TPE, cholestyramine, and dexamethasone. But none of the measures successfully normalize her thyroid function. So she was put on PTU as there was no alternative and she tolerated it well, thyroid function improved gradually, and she was found to be nearly euthyroid on follow-up at two weeks and there was no agranulocytosis. On searching the literature, there were only very few case reports published in the past that showed switching from one thionamide to another in case of drug-induced agranulocytosis. This case substantiates that it might be safe to substitute one thionamide over another if other definitive therapy modes are contraindicated or unavailable.

Conclusions

This case highlights the challenges in treating thyrotoxicosis prior to elective RAI ablation in a patient with CBZ-induced agranulocytosis and also highlights that PTU might be used in a patient in a special situation like CBZ-induced agranulocytosis when no other option is available but large scale study needed.

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Disclosure

The authors have no multiplicity of interest to disclose.

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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 assent was taken from the patient.

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