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Agranulocytosis: A rare side effect of carbimazole and the function of Cholestyramine in Hyperthyroidism

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ABSTRACT

Agranulocytosis is a rare side effect of antithyroid drugs that usually develops within the few months after starting treatment. We report a 45-year-old Indian female who presented to the hospital with shortness of breath, lethargy, decreased appetite, pharyngitis, and fever after used of Carbimazole 30mg OD for 2 months due to hyperthyroidism which was prescribed by her clinician. Her full blood count revealed neutropenia with a count of 0.03 × 109/L. Carbimazole was discontinued and she was given antibiotics. Cholestyramine was used to treat her hyperthyroidism. In conclusion, agranulocytosis induced by the Carbimazole is important to recognise and treat early to prevent morbidity and mortality.

Keywords: Carbimazole, Hyperthyroidism, Cholestyramine, Agranulocytosis, Neutropenia

INTRODUCTION

Hyperthyroidism is a very common disease, most likely caused secondary to Graves's disease followed by toxic multi-nodular goitre. Thioamide drugs are one of the medicine categories used in the treatment of hyperthyroidism. It inhibits the thyroid peroxidases that catalyze the iodination of tyrosine residues in thyroglobulin and the oxidative coupling of iodinated tyrosines. Inhibition of iodination is competitively antagonized by iodide at low drug concentrations, but not at higher drug concentrations [1]. It has been suggested that it also reduces the autoimmunity that underlies the Graves' disease. Thioamides, which have been in use for more than half a century, remain cornerstones in the management of hyperthyroidism [2]. Most patients tolerate treatment well, but some may develop life-threatening side effects such as agranulocytosis [3,4,5]. Agranulocytosis is the most severe adverse hematologic reaction associated with the Thioamides. Agranulocytosis typically develops within the first 3 months of treatment, although it can occur at any time and as late as 12 months after starting Thioamide therapy [6].

The prevalence of agranulocytosis is about 0.2-0.5%. The risk factors for agranulocytosis are unknown [7]. There is no predilection for either gender, and the reaction may be idiosyncratic, or dose related. Some reports suggest that patients older than 40 years or those taking high dosages of methimazole (e.g., >40 mg/day) might be more susceptible than those on any dosage of propylthiouracil [8]. If agranulocytosis is diagnosed, the drug should be discontinued, the patient monitored for signs of infection, and antibiotics instituted if necessary [9]. Although some cases of granulocytopenia have resolved with substitution or continuation of Thioamides, the risks of drug re-challenge clearly outweigh the benefits, and other treatments should be instituted [2].

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Case Report:

A 45-year-old Indian woman with the known past medical history of hyperthyroidism was hospitalized in

Malaysia hospital with shortness of breath, lethargy, decreased appetite, pharyngitis, and fever. She suffered also from major weight loss; her weight dropped down from 56 Kg to 47 Kg within 2 months. This incidence encouraged her to see a doctor and got the diagnosis of hyperthyroidism in April 2019. She denied any history of palpitation, sweating, or diarrhoea. She denied any allergy to medications. Her vital signs showed BP 92/58 mmHg, heart rate 132 bpm, respiratory rate 20 breaths/min, oxygen saturation 97%, weight 47 kg, and height of 161 cm. The patient is a non-smoker, non-alcoholic and does not abuse drugs. She is married and has one son (12 years old). Her occupation was a fruit seller. Her past medication history consists of once-daily Propranolol 20 mg and Carbimazole 30 mg.

Her blood test showed the values for Hemoglobin 8.2 mg/dl, total leukocyte counts 1240/mm ^{3}, platelet 166,000 per µL, SCr 47 µmol/L, K 3 mEq/L, PO4 0.3 mmol/L, and Albumin 20 g/litre. Differential leukocyte counts - Neutrophil 3 %, Lymphocytes 80 %, Monocytes (M) 2 %, Basophils 0 %, peripheral blood smear showed normocytic normochromic RBC series, reduced total leukocyte count with neutropenia. Initial thyroid function test showed TSH value of 0.27 mlU/L (0.4 - 4.5 mlU/L), FT4 of 30.47 pmol/L (9.0-24.0 pmol/L), and FT3 of 1.93 pmol/L (2.2 - 5.4 pmol/L).

The patient was diagnosed with neutropenic sepsis secondary to carbimazole induced agranulocytosis. As Carbimazole was the drug responsible for current patient status, it was discontinued, and she was treated in the ward from 9 to 24/06/2019 as shown in Table 1.

Table 1.Medication history of the patients from 9 to 24/06/2019

Date	Name of the drug (Brand/Generic)	Dose	Route	Frequency	Stop date
09/06/2019	Rocephin (ceftriaxone)	2g	IV	OD	10/06/2019
10/06/2019	Tazocin (Piperacillin/tazobactam)	4.5g	IV	QID	24/06/2019
20/06/2019	Propranolol	20mg	Oral	OD	
22/06/2019	Cholestyramine	4g	Oral	TDS	
13/06/2019	Vit.C		Oral	OD	
18/06/2019	Lithium	350 mg	Oral	BID	21/06/2019
12/06/2019	Ferrous Fumarate	200 mg	Oral	BID	
10/06/2019	Dexamethasone	2 mg	Oral	QID	10/06/2019
09/06/2019	Lugols Solution		Oral	TDS	10/06/2019
10/06/2019	KH2PO4		IV	OD	12/06/2019
09/06/2019	MgSo4		IV	BID	11/06/2019
09/06/2019	Propylthiouracil (PTU)	600 mg	Oral	TDS	09/06/2019
09/06/2019	Hydrocortisone	200 mg	Oral	TDS	11/06/2019
11/06/2019	Noradrenaline		IV	OD	11/06/2019
09/06/2019	Paracetamol	1 g	Oral	OD	24/06/2019
09/06/2019	Thiamine	200 mg	IV	OD	10/06/2019
11/06/2019	KCL	1 mg in 100 cc	IV	OD	11/06/2019
12/06/2019	0.2% chlorohexidine		Oral	TDS	24/06/2019
12/06/2019	Slow K	1.2 g	IV	BID	12/06/2019
09/06/2019	Rocephin (ceftriaxone)	2g	IV	OD	10/06/2019
09/06/2019	MgSo4		IV	BID	11/06/2019
09/06/2019	PTU	600 mg	Oral	TDS	09/06/2019

Date	Name of the drug (Brand/Generic)	Dose	Route	Frequency	Stop date
09/06/2019	Hydrocortisone	200 mg	Oral	TDS	11/06/2019
09/06/2019	Lugols Solution		Oral	TDS	10/06/2019
09/06/2019	Paracetamol	1 g	Oral	OD	24/06/2019
09/06/2019	Thiamine	200 mg	IV	OD	10/06/2019
10/06/2019	Tazocin (Piperacillin/tazobactam)	4.5g	IV	QID	24/06/2019
10/06/2019	Dexamethasone	2 mg	Oral	QID	10/06/2019
10/06/2019	KH2PO4		IV	OD	12/06/2019
11/06/2019	Noradrenaline		IV	OD	11/06/2019
11/06/2019	KCL	1 mg in 100 cc	IV	OD	11/06/2019
12/06/2019	Ferrous Fumarate	200 mg	Oral	BID	
12/06/2019	0.2% chlorohexidine		Oral	TDS	24/06/2019
12/06/2019	Slow K	1.2 g	IV	BID	12/06/2019
13/06/2019	Vit.C		Oral	OD	
20/06/2019	Propranolol	20mg	Oral	OD	
22/06/2019	Cholestyramine	4g	Oral	TDS	

Her condition improved within seven days of stopping the Carbimazole. On 17/06/2019 total white blood cell and neutrophil counts reverted to near normal range and symptoms like shortness of breath, lethargy, decreased appetite, pharyngitis, and fever disappeared. The patient was discharged from the hospital after 14 days and her discharge medications are shown in Table 2.

Table 2. Patient discharged medications list

S. No	Drug	Dose	Frequency
1.	Cholestyramine	4 g	TDS
2.	Prednisone (0.5/kg)	20 mg	OD
3.	Propranolol	20 mg	OD
4.	Ferrous Fumarate	400 mg	OD
5.	Vit.C	100 mg	OD
6.	Vit.B	10 mg	OD
7.	Folate	5 mg	OD

Discussion:

Agranulocytosis is a rare but serious complication of antithyroid drug therapy. A study done by Van der Klauw *et al* [9]reported a relative risk of agranulocytosis among 115 for patients who received the antithyroid drugs (ATD), was found the highest risk among all others evaluated pharmacological agents. Similarly, in a study done by Tajiri *et al*., among 15,398 Japanese patients with Graves' disease, there was no difference in the incidence of agranulocytosis between patients receiving propylthiouracil and those receiving the methimazole [10]. The result of this case report is consistent with Van der Klauw et al and Tajiri et al [9,10].

, A study done by Nakamura *et al* [11] reported an analysis of 754 cases that published of ATD induced agranulocytosis in Japan[11], the mean age of onset was 43.4

± 15.2 years and indicated that the females were more affected than males (6.3:1 ratio). Another, study done by Yang *et al* [12] reported an analysis of 114 cases with ATD induced agranulocytosis diagnosed in a single Chinese centre revealed a higher female-to-male ratio (10.4:1) and similar age of onset (41.7 ± 12.3 years) [12]. Agranulocytosis usually develops in the first 3 months after antithyroid drugs therapy is initiated [11]. In Japan, a 754 retrospectively reviewed cases of agranulocytosis after use of ATD found that more than 70% of patients who developed this side effect within 2 months, and nearly 85% showed this effect within 3 months[9]. The current case report of agranulocytosis manifest with 45 year old female patient and this consistent with the finding of Nakamura *et al*[11] and Yang *et al*[12].

The current case may have a difference in time of onset and may be related to the disease mechanism, with the immune-mediated process that leads to the more rapid destruction of neutrophils as opposed to direct toxicity. The previous studies recognised that the mean duration of treatment with propylthiouracil, carbimazole and methimazole needed to cause agranulocytosis was found to be 36, 41, and 42 days, respectively [13]. Agranulocytosis can manifest not only after the first treatment with ATD but also in later courses. It can manifest up to eight courses later (with either the same or a different ATD) but usually occurs 5 months after finishing the previous treatment [14]. Another study done by Kim *et al* reported severe agranulocytosis developed after 3 weeks on carbimazole treatment[15]. In the present case report, agranulocytosis manifests 2 months after treatment with Carbimazole 30 mg OD. In summary, Agranulocytosis is life-threatening, but treatable within the opportunity, and the most important lesson for physicians in the future is to remain vigilant for ATD induced agranulocytosis regardless of treatment duration or dose.

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ندرة المحببات: تأثير جانبي نادر للكربيمازول ووظيفة الكوليستيرامين في فرط نشاط الغدة الدرقية

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ملخص

ندرة المحببات هو أحد الآثار الجانبية النادرة للأدوية المضادة للغدة الدرقية التي عادة ما تتطور في غضون بضعة أشهر بعد بدء العلاج. أبلغنا عن امرأة هندية تبلغ من العمر 45 عامًا قدمت للمستشفى مع ضيق في التنفس والخمول وتراجع الشهية والتهاب البلعوم والحمى بعد تناولها لـ كاربيمازول 30 ملغ مرة يوميا لمدة شهرين بسبب فرط نشاط الغدة الدرقية الذي وصفه الطبيب السريري لها. وعند كشف تعداد دمها الكامل وجد قلة العدلات بنسبة 0.03 × 109 / لتر. تم إيقاف كاربيمازول وتم إعطاؤها المضادات الحيوية. تم استخدام كوليستيرامين لعلاج فرط نشاط الغدة الدرقية لها بدلاً من كاربيمازول. في الختام ، ندرة المحببات التي يسببها كاربيمازول من المهم التعرف عليها والعلاج في وقت مبكر لمنع المراضة والوفيات.

الكلمات الدالة: كاربيمازول ، فرط نشاط الغدة الدرقية ، كوليستيرامين ، ندرة المحببات ، قلة العدلات.

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