

CARBIMAZOLE-RELATED AGRANULOCYTOSIS IN PREGNANCY – A CASE REPORT

Lim SS, Shireene V, Vijay A, Tan TBA, Rokiah P, Chan SP

Department of Medicine (Endocrinology), Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

ABSTRACT: We report a 33-year-old Malay lady who presented with fever, tonsillitis and pharyngitis a month after initiation of antithyroid therapy (carbimazole 15 mg tds) for thyrotoxicosis by her general practitioner. She was still clinically and biochemically thyrotoxic but not in thyroid storm. At that time, she was also confirmed to be four weeks pregnant. Her full blood count revealed neutropaenia with an absolute neutrophil count of $0.036 \times 10^9/L$. Bone marrow aspirate and trephine were compatible with carbimazole-related agranulocytosis. Carbimazole was discontinued and she was given broad spectrum antibiotics and Granulocyte Colony Stimulating Factor (GCSF), to which she responded. Verapamil was used for symptomatic heart rate control instead of beta-blockers as she had a history of bronchial asthma. The patient subsequently opted for termination of pregnancy after which she was given radioactive iodine I^{131} (10 mCi) for definitive therapy of her thyrotoxicosis. In conclusion, carbimazole-related agranulocytosis is an important entity to recognise and treat early to prevent morbidity and mortality. Termination of pregnancy was carried out as the treatment given during the episode of agranulocytosis may have negative effects on foetal viability and growth. (*JUMMEC 2007; 10(1): 34-38*)

KEYWORDS: Thyrotoxicosis, carbimazole, agranulocytosis, neutropaenia, pregnancy, granulocyte colony stimulating factor

Introduction

Hyperthyroidism in pregnancy is relatively rare, occurring in 0.2% of pregnancies in the US, with the most common cause being pre-existing Graves' disease (1-4). Uncontrolled hyperthyroidism can adversely affect not only the mother's health, but can cause congenital abnormalities, foetal goitre, thyrotoxicosis, neonatal Graves' disease, and an increase in foetal mortality (3).

Medical treatment for thyrotoxicosis consists of carbimazole (methimazole) or propylthiouracil. In the US, propylthiouracil is more popular whereas in the UK and Europe, carbimazole is more frequently used. Aplasia cutis has been described in about 20 infants exposed *in utero* to methimazole (carbimazole) (5). The risk of occurrence when using this medication is unknown, but no adverse reactions to the foetus have been described with the use of propylthiouracil. Thus, propylthiouracil is preferred to carbimazole (methimazole) in pregnancy (5).

Carbimazole is a prototype drug in the thionamide group, which is commonly used for the treatment of thyrotoxicosis. It is very effective in the treatment of thyrotoxicosis but, like any other drug, it has side-effects, namely, fever, skin rashes, arthralgia and hepatitis. Carbimazole-related agranulocytosis is rare with an incidence of 0.3%-0.6% but mortality is less than 1 in 10,000 (6) treated patients as compared to 20% in the past (7). Recent studies have shown that the mechanism of antithyroid drug-related agranulocytosis is more of an immunological phenomenon, rather than a direct toxic effect of the antithyroid drugs (ATD) (8). Patients who develop agranulocytosis are susceptible to a variety of infections, some of which are potentially fatal.

Correspondence:

Dr Lim SS

Department of Medicine (Endocrinology)

Faculty of Medicine

University of Malaya

50603 Kuala Lumpur, Malaysia

Email address: limss72@hotmail.com

In short, carbimazole-related agranulocytosis is associated with significant morbidity and mortality. This adverse effect is more complicated in a pregnant individual. Here, we are not only concerned about the thyroid status of the mother but also the effects of the drugs for example, GCSF on the foetus while managing the agranulocytosis.

We would like to illustrate the above by reporting a case of a pregnant patient with thyrotoxicosis who developed carbimazole-related agranulocytosis.

Case Report

A 33-year-old woman with a background history of bronchial asthma presented to the University Malaya Medical Centre with a one-week history of fever, vomiting and diarrhoea. This was preceded by a non-resolving sore throat for a month. At that time, she had been diagnosed by her general practitioner to have thyrotoxicosis, having presented with the classical features, i.e. tremors, palpitation, heat intolerance and weight loss of 12 kg over the previous five months. She was started on carbimazole 15 mg tds.

Clinical examination revealed that she was febrile (38.2°C) (Figure 1a), tachycardic (120 beats/min) and tremulous with an underlying small diffuse goitre. She was not, however, in thyroid storm. There was also enlargement of the tonsils with white exudates.

White blood cell count on admission was $1.2 \times 10^9/L$ with an absolute neutrophil count of $0.036 \times 10^9/L$ (Figure 1b). Bone marrow examination showed mildly depressed granulopoiesis with maturation arrest at the myelocyte stage in keeping with drug-induced agranulocytosis (Slide 1). At that time, her free thyroxine was 40.4 pmol/L and Thyroid Stimulating Hormone (TSH) was < 0.01 mIU/mL (Figure 2). She was also found to be four weeks' pregnant based on her account on a period of amenorrhoea and this was confirmed by a positive urine pregnancy test and an elevated serum Beta Human Chorionic Gonadotrophin. Transvaginal ultrasound also confirmed an intrauterine yolk sac and right corpus luteal cyst. She was gravida 5, para 2 with 2 previous abortions.

She was started on verapamil 40 mg bd for symptomatic control of her heart rate. Beta-blockers were avoided as she had a past history of bronchial asthma. She was also treated with intravenous piperacillin-tazobactam 4.5 g three times daily empirically for febrile neutropaenia. Her fever resolved after three days of antibiotics. As her white cell counts failed to improve, she was given 300 µg of subcutaneous GCSF. Her neutrophil count rose to more than $0.5 \times 10^9/L$, 5 days after GCSF which corresponds to 9 days after stopping carbimazole. The white cell count continued to rise to $1.9 \times 10^9/L$ and finally reached $5.9 \times 10^9/L$ (Absolute Neutrophil Count [ANC] of 49%) (Figure 1b). As all blood and urinary cultures were negative, the antibiotic was stopped after one week. The patient's condition gradually improved but she remained thyrotoxic.

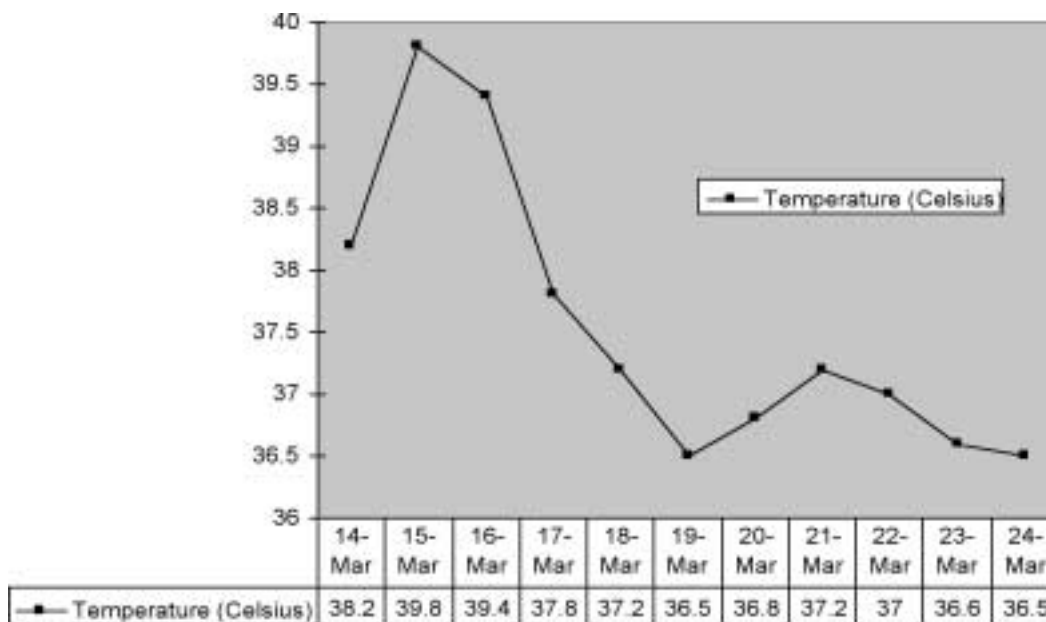


Figure 1a. Temperature profile of patient

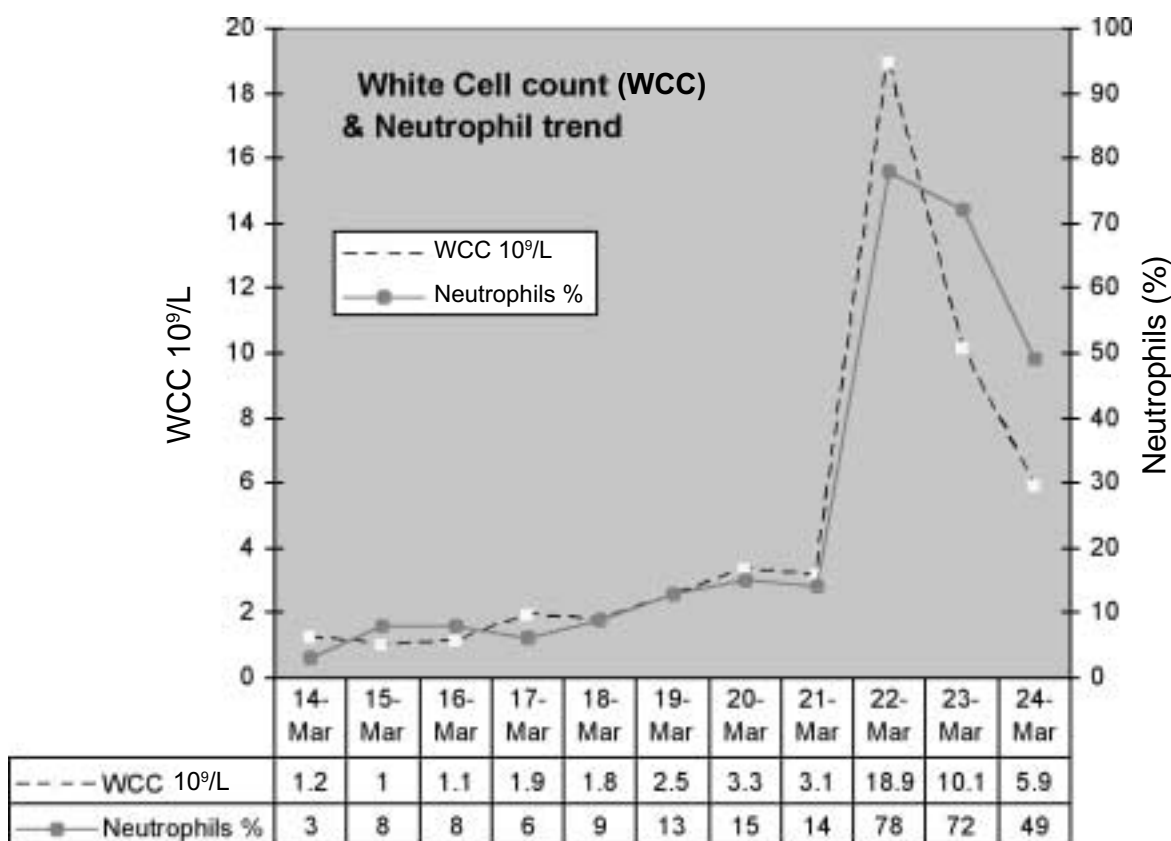
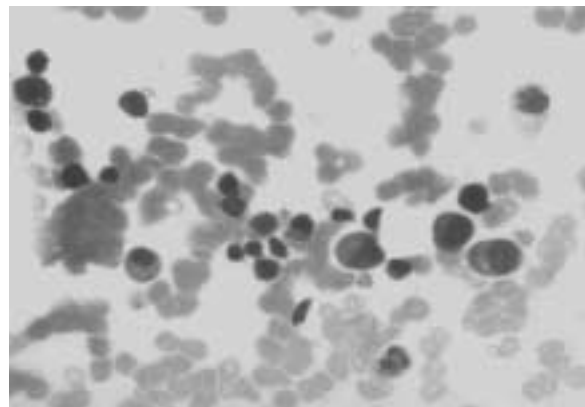


Figure 1b. White Cell count and neutrophil trend of patient

Subsequent management was comprehensively discussed by a multidisciplinary team that included endocrine, obstetrics and nuclear medicine divisions, together with the patient and her husband. Issues discussed included the potential risks of recurrent agranulocytosis with reinstatement of thionamide therapy, the risk of untreated and uncontrolled thyrotoxicosis to the mother and foetus in pregnancy. The effects of the various treatment options on the foetus were also discussed – for example, GCSF is known to cause organogenesis associated with increased foetal resorption, genitourinary bleeding, developmental abnormalities and decreased body weight if administered to pregnant rabbits at doses of 80 mcg/kg/day (9). However, since there are no adequate and well-controlled studies in pregnant women, the effect, if any, of GCSF on the developing human foetus or the reproductive capacity of the mother is unknown.

Radioactive iodine, on the other hand, being the most widely recommended definitive treatment with thyroidectomy being the second (but widely used) choice, could cross the placenta and destroy normal thyroid cells in the baby (10) as the effects of radioiodine which has a half life of up to nine days, may persist indefinitely (11). Therefore, the patient finally, opted

for termination of pregnancy when she was stabilised followed by radioactive iodine ablative therapy (10 mCi), which she underwent uneventfully a month after the termination. She was hospitalised during the radioactive iodine ablative therapy for a week as it may precipitate thyroid storm. Verapamil was continued to control her heart rate until she became euthyroid. At follow-up six months later, she was hypothyroid requiring thyroxine replacement.



Slide 1. Histology of bone marrow with depressed granulopoiesis and maturation arrest at the myelocyte stage

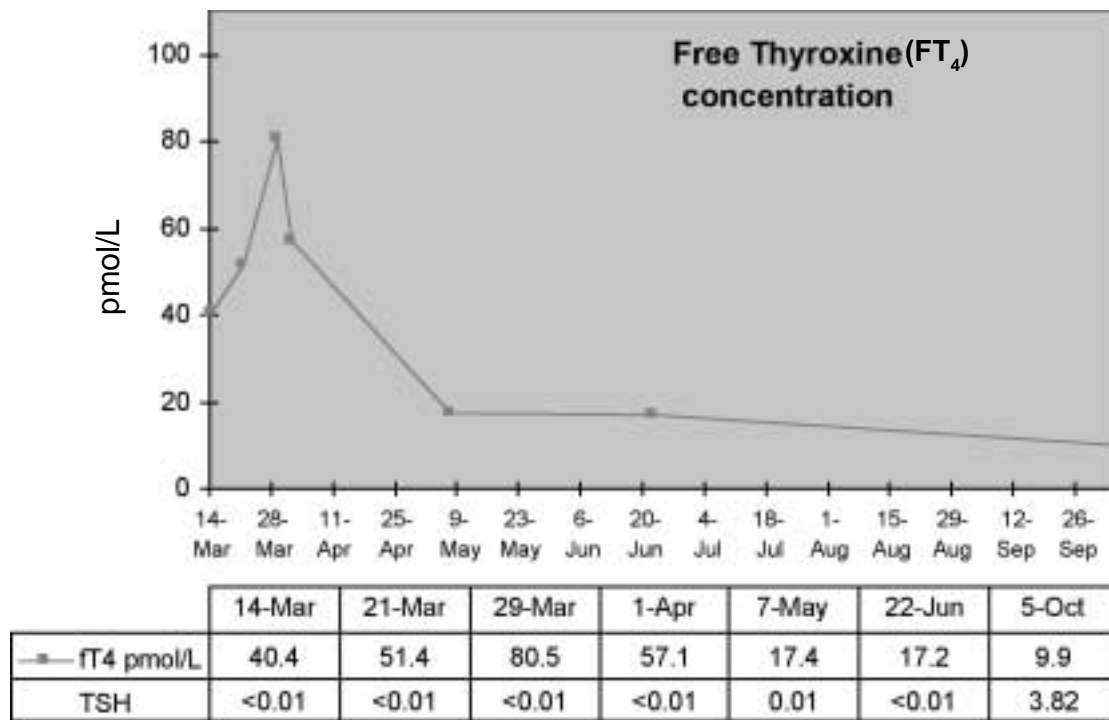


Figure 2. Free Thyroxine concentration

Discussion

This was a rare and complicated case of antithyroid drug-related agranulocytosis as it occurred in a pregnant lady who had bronchial asthma. The duration of treatment with carbimazole to the onset of agranulocytosis is important to note. Agranulocytosis (ANC < 0.5 x 10⁹/L) is an idiosyncratic reaction that can occur anytime during treatment with thionamides but usually happens within 1- 2 months after starting treatment (12). However, agranulocytosis occasionally can develop even though the total white blood cell count remains within normal range and therefore, it is important to perform differential counts (13).

Recognition of early symptoms is the first step to diagnosis. A history of fever a month after commencing carbimazole with an absolute neutrophil count of 0.5 x 10⁹/L and bone marrow histology of mildly depressed granulopoiesis with maturation arrest at the myelocyte stage is consistent with carbimazole-related agranulocytosis. Although it is known that relative lymphocytosis and relative monocytosis, with a normal or slightly low total white cell count, constitute the characteristic blood findings of Graves' disease; significant pancytopenia with leukocyte counts under 3 x 10⁹/L and neutrophils under 2 x 10⁹/L occasionally occurs, and if unrelated to drug therapy, tends to recover during treatment (14). With regard to this case, the white cell count did not improve during carbimazole therapy. Upon withdrawal of carbimazole the white

cell count improved. As such, we therefore concluded that neutropaenia was due to carbimazole rather than the disease itself.

The infection associated with carbimazole-induced agranulocytosis usually starts from the oropharynx, either acute pharyngitis or tonsillitis. In some clinical studies, the most commonly isolated microorganism is *Pseudomonas aeruginosa* (8).

The management of carbimazole-induced agranulocytosis has evolved over the years. The introduction of GCSF has led to quicker recovery of granulocytes. Tajiri J, Noguchi S, Murakami N (15) published a prospective study on the use of GCSF measurements four hours after injections of GCSF. It concluded that GCSF measurements four hours post-administration were useful for detecting recovery from ATD-induced granulocytopenia or agranulocytosis and for predicting disease severity (15). Hence, this implies the speedy action of GCSF in reducing the incidence of fatal complications (12).

The offending drug needs to be stopped immediately. Broad spectrum antibiotics with pseudomonal coverage have to be started empirically.

Because of her past history of bronchial asthma, beta-blockers could not be given to alleviate her adrenergic symptoms. Verapamil, a calcium channel blockers were given to control her heart rate as an alternative.

Although secondary amenorrhoea is a common feature of thyrotoxicosis, and this patient reported delayed menses, testing for pregnancy revealed that she was pregnant.

Termination of pregnancy was contemplated as GCSF's effect on human pregnancy is unknown. Although piperacillin and tazobactam were not teratogenic in animal studies, both antibiotics cross the human placenta. Their effects on pregnancy in humans are also unknown (16). As for verapamil, it readily crosses the placenta and has been shown to cause foetal bradycardia, heart block, depression of contractility, and hypotension (17).

Termination of pregnancy is preferably done in the first trimester as the risk of bleeding is lower. After the termination, definitive therapy for her thyrotoxicosis was discussed. The patient opted for radioactive iodine (10 mCi) after termination of pregnancy. The treatment of thyrotoxicosis with radioactive iodine is much more efficacious than medical or surgical modalities. Furthermore, it is by far the most cost-effective and has no harmful effects (18). Surgery, on the other hand, is currently only employed in a minority of patients. Indications for surgery include thyrotoxic individuals who are allergic to thionamides and unable to take radioiodine because of pregnancy, youth, massive thyromegaly with compressive symptoms or personal choice (19). Its limited indication is due to a somewhat higher incidence of recurrent laryngeal nerve damage and permanent hypoparathyroidism (20). Propylthiouracil was not considered as there is cross reactivity of as high as 50 per cent with carbimazole (21).

In summary, patients ought to be informed of the side effects of carbimazole – in particular agranulocytosis. Although it is rare, patients should be told to look out for early warning signs in terms of symptoms and duration of therapy in order to seek early and prompt treatment. Agranulocytosis is life-threatening but treatable within the window of opportunity.

References

- Lazarus JH. Epidemiology and prevention of thyroid disease in pregnancy. *Thyroid* 2002; 12:861-5.
- Schroeder BM. ACOG practice bulletin on thyroid disease in pregnancy. *Am Fam Physician* 2002; 65: 2161-2.
- Mestman JH. Hyperthyroidism in pregnancy. *Clin Obstet Gynecol* 1997; 40:45-64.
- Glinoe D. Thyroid hyperfunction during pregnancy. *Thyroid* 1998; 8:859-64.
- Gleicher N, Galbraith RM, Elkayam U, *et al*. Principles and Practice of Medical Therapy in Pregnancy. 3rd ed. Norwalk, Conn: Appleton and Lange. 1998; 436-41.
- Burrow GN, Golden LH. Maternal Thyrotoxicosis. *Endocrinology of Pregnancy, Thyroid Disease During Pregnancy*. www.endotext.org/pregnancy. (accessed on 28 May 2007).
- Tajiri J, Noguchi S, Okamura S, *et al*. Granulocyte colony-stimulating factor treatment of antithyroid drug-induced granulocytopenia. *Arch Intern Med* 1993; 153:509-14.
- Sheng WH, Hung CC, Chen YC, *et al*. Antithyroid drug-induced agranulocytosis complicated by life-threatening infections. *Q J Med* 1999; 92:455-61.
- Neupogen - product information leaflet 3/2007.
- Hyperthyroidism and Pregnancy. *Endocrine Disorders and Endocrine Surgery*. www.endocrineweb.com/pregnancy. (accessed 28 May 2007).
- Berg GEB, Michanek AMK, Holmberg ECV, *et al*. Iodine-131 treatment of hyperthyroidism: Significance of effective half-life measurements. *J Nucl Cardiol* 1996; 37(2):228-32.
- Lee CH, Liang RHS. Antithyroid drug-induced agranulocytosis. *Hong Kong Med J* 1999; 5: 394-6.
- De Groot LJ. Graves' - Anti-Thyroid Therapy. *Diagnosis and Treatment of Graves' Disease*. www.thyroidmanager.org/chapter11/chapter11.html. (accessed on 28 May 2007).
- Lima CS, Wittmann DE, Castro V, *et al*. Pancytopenia in untreated patients with Graves' disease. *Thyroid* 2006; 16(4):403-9.
- Tajiri J, Noguchi S, Murakami N. Usefulness of granulocyte count measurement four hours after injection of granulocyte colony-stimulating factor for detecting recovery from antithyroid drug-induced granulocytopenia. *Thyroid* 1997; 7(4): 575-8.
- Bryson HM, Brogden RN. Piperacillin/Tazobactam. A review of its antibacterial activity, pharmacokinetic properties, and therapeutic potential. *Drugs* 1994; 47(3):506-35.
- Mason BA, Ricci-Goodman J, Koos BJ. Adenosine in the treatment of maternal paroxysmal supraventricular tachycardia. *Obstet Gynecol* 1992; 80 (3 Pt 2):478-80.
- Qari FA, Naser TA, Hashim IM, *et al*. Outcome of thyrotoxicosis treatment with 3 different modalities. *Saudi Med J* 2001; 22(10):907-9.
- Mittendorf EA, McHenry CR. Thyroidectomy for selected patients with thyrotoxicosis. *Arch Otolaryngol Head Neck Surg* 2001; 127:61-5.
- Fisher JN. Management of thyrotoxicosis. *South Med J* 2002; 95(5):493-505.
- Cooper DS. Drug therapy: antithyroid drugs. *NEJM* 2005; 352(9):905-17.