CARBIMAZOLE-RELATED AGRANULOCYTOSIS IN PREGNANCY – A CASE REPORT

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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 bronchal asthma. The patient subsequently opted for termination of pregnancy after which she was given radioactive iodine $^{131}$I (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 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.

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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. This was treated off 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 × 10⁹/L, 5 days after GCSF which corresponds to 9 days after stopping carbimazole. The white cell count continued to rise to 1.9 × 10⁹/L and finally reached 5.9 × 10⁹/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.

White blood cell count on admission was 1.2 × 10⁹/L with an absolute neutrophil count of 0.036 × 10⁹/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 mlU/mL (Figure 2). She was also found to be four weeks pregnant based on her account on a period of ammenorrhoea 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 × 10⁹/L, 5 days after GCSF which corresponds to 9 days after stopping carbimazole. The white cell count continued to rise to 1.9 × 10⁹/L and finally reached 5.9 × 10⁹/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](image-url)
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 reinstitution 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 radiiodine 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](image-url)
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 10^9/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 10^9/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 pancytopaenia with leukocyte counts under 3 x 10^9/L and neutrophils under 2 x 10^9/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 granulocytopaenia 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 blocker was 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