*Asian Jr. of Microbiol. Biotech. Env. Sc. Vol. 21, No. (4) : 2019 : 837-839*

***ISSN-0972-3005***

# ANTITHYROID DRUG-INDUCED AGRANULOCYTOSIS, A CASE REPORT

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(Received 10 May, 2019; accepted 15 July, 2019)

***Key words :*** **A**dverse effect, Antithyroid drug, Agranulocytosis

**Abstract** – Hyperthyroidism is a common problem in general internal medicine practice. Current treatments of hyperthyroidism involve antithyroid drugs (ATD) medications. Agranulocytosis is a rare adverse effect of ATD, usually occurs within the first 23 months of treatment. However, serious life threatening adverse effects may occur, mainly due to severe systemic infection if appropriate medical intervention is not given immediately. In this case report, a 29 year old female, developed agranulocytosis following the treatment for thyrotoxicosis. The present case report aims to increase the awareness of the adverse effect of ATD treatment and warns that ATD should be used with caution.

## INTRODUCTION

Antithyroid drugs such as methimazole and propylthiouracil are essential in the management of hyperthyroidism. In the treatment of thyrotoxicosis, the most serious adverse effect of ATD is agranulocytosis, a marked decrease in the white blood cell count. White blood cells help fight infections, so agranulocytosis can result in severe infections, a serious complication which may lead to fatal complications. It is standard practice to advise patients about this side effect and to instruct them to stop the causative drug immediately to prevent further damage. If patients at risk for this severe side effect could be identified, other options for treatment such as radioactive iodine or surgerycould be chosen. It is good practice to educate patients taking antithyroid drugs about agranulocytosis. The aim of this report is to increase awareness in physicians that ATD can induce agranulocytosis and to demonstrate that ATD should be used with caution.

## CASE REPORT

A 29 year old female was admitted to hospital complaining of ongoing fatigue, palpitations, and tremors for a month. Upon first admission, she was found to have heart rate of 110 beats per minute, she was afebrile, thyroid stimulating hormone (TSH):0.08 uIU/mL and thyroxine (T4) of 7.64 ng/dL, suggestive of hyperthyroid. Initial management included methimazole 20 mg daily and propranolol 20 mg three times daily. After 25 days, the patient returned to the emergency department complaining of fever and sore throat. By the time she presented to the hospital, she was febrile (39$^{o}$C). A chest x-ray and abdominal ultrasound were performed showing no abnormalities. Laboratories demonstrated a white blood cell count of 800/µL and neutrophil count of 0.0/µL. Differential showed: 0.0 % neutrophils, 97.4 % lymphocytes, 2.6 % monocytes, 0.0 % eosinophils, 0.0 % basophils. ATD-induced agranulocytosis was suspected. Because of serious concern to ATD-induced agranulocytosis, she was advised to discontinue methimazole treatment promptly. A granulocyte colony-stimulating factor and antibiotics were provided. After 2 weeks, white blood cell count recovered to 11.000/ µL, and the absolute neutrophil count recovered to 67.6 /µL. The symptoms also resolved. The patient's hyperthyroidism was ultimately managed with a total thyroidectomy and thyroid replacement therapy.

## DISCUSSION

Antithyroid drugs, especially thioamides (propylthiouracil, methimazole and carbimazole) have adverse hematological effects, ranging from

mild leukopenia to agranulocytosis and aplastic anemia (Sun *et al*., 2009). The frequency of agranulocytosis is between 0.03 and 0.18% of patients with Graves' disease receiving antithyroid drugs (Robinson *et al*., 2014). The first death associated with ATD therapy dates from 1952, when a patient receiving methimazole developed high fever and dyspnea and eventually died of bilateral pneumonia (Vicente *et al*., 2017). Drug-induced agranulocytosis has been defined as an absolute neutrophil count (ANC) < 500/μL of blood (Vicente *et al*., 2017). To find a sustained causal relationship between agranulocytosis and ATD, the following three criteria may be used: (1) onset of agranulocytosis during treatment or within 7 days of previous exposure to the same drug and complete recovery with ANC >1500/μL within 1month of discontinuation of the drug; (2) reoccurrence ofagranulocytosis upon re-exposure to an offending drug; and (3) criteria of exclusion: any history of congenital neutropeniaor immune neutropenia; recent infectious disease; recent chemotherapy, radiotherapy, or immunotherapy; and an underlying hematological disease (Vicente *et al*., 2017).

The incidence of ATD-induced agranulocytosis in patients with hyperthyroidism is rare; however, serious and potentially life-threatening adverse effects may occur, mainly due to severe systemic infection if appropriate medical intervention is not given immediately. Although a higher dose of ATD and a longer drug treatment period might cause greater probability of agranulocytosis, this serious complication can occur at any time, even a lower dose of ATD cannot protect the patient from agranluocytosis (Huang *et al*., 2007). The methimazole package insert in Japan includes a strong warning to check blood counts every 2 weeks for the first 2 months of therapy (Nakamura *et al*., 2013). Using this, Tajiri reported that they successfully identified 78% of granulocytopenia cases before onset of symptoms by periodically checking blood counts (Tajiri *et al*., 1990). The major complaints from patients were fever (100%), sore throat (76.9%), chills (46.1%), cough (30.8%), and rhinorrhea (30.8%). Other symptoms (7% to 14%) were general malaise, oral ulcer, skin rashes, headache, palpitations and dysphagia (Huang *et al*., 2007). Antithyroid drug-induced agranulocytosis occurs most frequently in the first 3 months of treatment, but it can occur after long-term treatment (Sun *et al*., 2009). In the present study, a case of ATD-induced agranulocytosis is presented following continuous ATD treatment for 2weeks. Fever and sore throat were the most common symptomsThe pathogenesis of ATD-induced agranulocytosis is not completely understood. Various mechanisms for ATD-induced agranulocytosis have been determined, including direct toxic effects and immunological reactions (Sun *et al*., 2009). The direct toxic effects impact both mature circulating neutrophils and stem cells. The immunological reactions include immunoglobulin E-mediated hypersensitivity reaction, drug-induced immunoglobulin G and M responses, and neutrophil-drug complex (Sun *et al*., 2009). Patients with Graves' disease may be prone to develop this complication of antithyroid drug therapy because of underlying immunological abnormalities (Wall *et al*., 1984). However, the mechanism of ATD-induced agranulocytosis in patients with hyperthyroidism was demonstrated *in vitro* to be a drug-induced immune-mediated process rather than a direct toxic effect of ATD (Wall *et al*., 1984). Cheung *et al*., (2016) identified three genetic variants to be associated with ATD-induced agranulocytosis: rs652888 located in an intron of EHMT2, HLA-B*27:05 and HLA-B*08:01, thus patients that have certain genetic variants are at increased risk for ATD-induced agranulocytosis (Cheung *et al*., 2016). Screening forthese variants would help choose the best treatment for Graves' disease, although these markers are not ready to be put into general clinical use but suggest that this may be the case in the future. The risks of agranulocytosis in relation to the use of cardiovascular drugs were estimated in a population-based case-control study (Kelly *et al*., 1991). This study showed that propranolol was significantly associated with agranulocytosis, so our patient was advised to discontinue methimazole and propranolol treatment.

Mortality from ATD-induced agranulocytosis is low, however, of all the adverse reactions to antithyroid drugs, agranulocytosis and neutropenia account for 49% of mortality (Sun *et al*., 2009). Given that the highest risk of agranulocytosis is in the first 3 months after starting antithyroid drug medication, efforts to educate and remind patients are best concentrated in this initial phase of treatment (Robinson *et al*., 2014). Treatment starts with the identification and immediate discontinuation of the causative agent to prevent further damage. Granulocytes could reappear in the peripheral blood between few days to three weeks, after

discontinuation treatment but returns to normal shortly thereafter (Rosove *et al*., 1977). Granulocyte colony-stimulating factor (G-CSF) is a well-established treatment for reducing the duration of chemotherapy-induced neutropenia, and previous experience suggests that it may also have a role in the treatment of adverse events associated with nonchemotherapy medications (Birmingham *et al*., 2017). In our case, there was good prognosis after G-CSF and empirical antibiotic therapy. The recovery time for this patient after G-CSF therapy was 5 days. After recovery from agranulocytosis, doctors should be cautious about prescribing antithyroid drugs again, even another type of thioamide, due to common cross-reactions among thioamides (Sun *et al*., 2009). Radioiodine therapy or surgery may be better choices than the use of another type of antithyroid drug.

Inadequate knowledge about agranulocytosis among patients receiving anti-thyroid drug treatment is common, moreover the available information on the internet is variable and inconsistent (Robinson *et al*., 2014). Conducting a routine complete blood cell count is beneficial in alerting caregivers to the possibility of agranulocytosis. All patients with thyrotoxicosis must be warned that their white blood cells and differential counts should be checked immediately whenever the prodromes of ATD-induced agranulocytosis (e.g. fever, sore throat) symptoms occur during treatment, especially within the first 3 months of medication (Huang *et al*., 2007). For such patients who present with neutropenia, all ATD should be promptly discontinued.

## CONCLUSION

Agranulocytosis is a rare but serious complication of anti thyroid drug (ATD) therapy. Although depression of the granulocyte count is reversible after the drug is discontinued, itis important to be aware ofto the clinical features of granulocytopenic reactions and providing every patient with sufficient information on agranulocytosis is critical.

## REFERENCES


Birmingham, A., Mancuso, C. and Williams, C. 2017. Use of granulocyte colony-stimulating factor in the treatment of methimazole-induced agranulocytosis: a case report. *Clin Case Rep.* 5 (10) : 1701–1705.

Cheung, C.L., Sing, C.W., Tang, C.S., Cheng, V.K., Pirmohamed, M., Choi, C.H. 2016. HLA-B*38:02:01 predicts carbimazole/methimazole-induced agranulocytosis. *Clin Pharmacol Ther*. 99 (5): 555-561.

Huang, C., Li, K., Wu, J., Wang, P. and Juang, P. 2007. Antithyroid Drug-induced Agranulocytosis: Report of 13 Cases. *Chang Gung Med J.* 30 : 242-248.

Kelly, J.P., Kaufman, D.W. and Shapiro, S. 1991. Risks of agranulocytosis and aplastic anemia in relation to the use of cardiovascular drugs: The International Agranulocytosis and Aplastic Anemia Study. *Clin Pharmacol Ther.* 49 : 330-341.

Nakamura, H., Miyauchi, A., Miyawaki, N. and Imagawa, J. 2013. Analysis of 754 Cases of Antithyroid Drug-Induced Agranulocytosis Over 30 Years in Japan. *J Clin Endocrinol Metab.* 98 : 4776–4783.

Robinson, J., Richardson, M., Hickey, J., James, A., Pearce, S.H., Ball, S.G., Quinton, R., Morris, M., Miller, M. and Perros, P. 2014. Knowledge of antithyroid drug-induced agranulocytosis. *Eur Thyroid J.* 3 (4) : 245–251.

Rosove, M.H. 1977. Agranulocytosis and anti thyroid drugs. *West J Med.* 126 (5): 339–343.

Sun, M.T., Tsai, C.H. and Shih, K.C. 2009. Antithyroid Drug-induced Agranulocytosis. *J Chin Med Assoc.* 72 (8) : 438-441.

Tajiri, J., Noguchi, S., Murakami, T. and Murakami, N. 1990. Antithyroid drug-induced agranulocytosis. The usefulness of rouine white blood cell count monitoring. *Arch Intern Med.* 150 : 621–624.

Vicente, N., Cardoso, L., Barros, L. and Carrilho, F. 2017. Antithyroid drug-induced agranulocytosis: State of the art on diagnosis and management. *Drugs R D.* 17 : 91–96.

Wall, J.R., Fang, S.L., Kuroki, T., Ingbar, S.H. and Braverman, L.E. 1984. *In vitro* immunoreactivity to propylthiouracil, methimazole and carbimazole in patients with Graves' disease: a possible cause of antithyroid drug-induced agranulocytosis. *J Clin Endocrinol Metab.* 58 (5) : 868-872.