Management of thyroid crisis in a patient with febrile neutropenia

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ABSTRACT

Introduction: Thyroid storm is a life-threatening complication of acute hyperthyroidism. The diagnosis of thyroid storm can only be based on its clinical manifestations, which include decreased consciousness, high fever, heart failure, diarrhea and jaundice. Antithyroid drug therapy (ATD) is one option for treating hyperthyroidism, along with surgery and radioactive iodine. ATD is thought to cause neutropenia through the agranulocytosis pathway. The most common symptoms are fever and sore throat accompanied by symptoms of a thyroid crisis. There is no specific method for predicting the appearance of febrile neutropenia caused by ATD. Routine complete blood counts in patients taking ATD should be performed. The diagnosis of febrile neutropenia due to ATD needs to be done immediately so that timely intervention can be carried out and reduce mortality.

Case Presentation: a 25 years old female with thyroid crisis and febrile neutropenia. Clinical findings in the patient include fever, decreased consciousness, palpitation, excessive sweat, diarrhea, nausea and vomiting, weight loss, and the laboratory findings of leukopenia and neutropenia of (leucocyte 1.03x10³/ul, neutrophil 1.90x10³/ul). Ultrasound examination of the thyroid reveals a thyroiditis image with multiple solid nodules. Blood smear examination reveals leukopenia with differential count examination of blood showed neutropenia, moderate lymphocytosis, erthyrocyte hypochromic micrositer, poikilocytosis ovalocyte, teardrop cell, fragments and target cell. Polychromasia and normoblast cells are not found.

Conclusion: Thyroid crisis refers to the clinical findings and thyroid hormone test results. There is no specific method to predict the appearance of febrile neutropenia caused by the antithyroid drug. Frequent blood tests must be done in patients who consume antithyroid drugs.

Keywords: thyroid crisis, febrile neutropenia, antithyroid drug therapy.


INTRODUCTION

A thyroid storm, also known as thyroid crisis, is a life-threatening complication of acute hyperthyroidism. This condition is caused by excessive thyroid hormone (thyrotoxicosis), which causes the involvement of a multistystem that happens spontaneously. Mortality rate caused by thyroid storm is estimated to be as many as 8-25% out of all patients, even though advanced medication and supportive care have been done. That is why early diagnosis and aggressive medication are important to reduce mortality.¹ Clinical manifestation of thyrotoxicosis may appear in the form of multiple organ decompensations, which are usually triggered by severe stress. The true mechanism and pathophysiology are not yet to be discovered. Several clinical manifestations include decreased consciousness, hyperthermia, heart failure, diarrhea and icterus.²

Diagnosis of thyroid storm needs clinical manifestation and the hypothesis of existing hyperthyroidism. Medical intervention in suspected patients with thyroid storm doesn’t need to wait for the laboratory findings of hyperthyroidism to occur. Thyroid function tests usually show a high level of FT³/FT⁴ and a low level of Thyroid Stimulating Hormone (TSH). For a thyroid storm to happen, it is not always accompanied by a high thyroid hormone level. Other laboratory findings may include hypercalcemia, hyperglycemia (due to the inhibition process of insulin release and increase of glycoegenolysis), abnormal liver function test (LFT) and low/ high white blood cell count level.³ Treatment of thyroid storm consists of supportive care such as intravenous fluid, oxygen therapy, cold blanket, acetaminophen, also special care for lowering the hyperthyroidism condition. Other factors, such as infection, must also be monitored during the treatment. Patients with thyroid storm should be placed in an intensive care unit with comprehensive monitoring of heart function and ventilation support if needed.³

The antithyroid drug is one option for hyperthyroidism treatment, in addition to surgery and radioactive iodium therapy. The long-term remission rate of hyperthyroidism is around 50% out of all patients with Graves disease treated with an antithyroid drug. Drugs frequently used are propylthiouracil, carbimazole and active metabolites of methimazole. In daily clinical practice, propylthiouracil is usually substituted by carbimazole and methimazole due to its
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Twenty-five years old Balinese woman came to the emergency department of Prof. Dr. I.G.N.G Ngoerah Hospital with a fever. Fever was felt since 1 day before the patient went to the hospital with the highest temperature measuring 39 degrees celsius. Fever responds well with antipyretic drug but fever rises again when the effect is gone. The patient also felt nausea and vomited up to 3-4 times. The vomit consists of fluid and undigested food. The patient also felt palpitation and headache, especially during activity. Diarrhea also happened 5-6 times during the illness with yellow color without mucous and blood visible. The patient admits that 14 kg of weight is lost during 1 year. The patient also felt a sore throat and blocked the nasal without excessive mucous. During the previous month the patient felt she was more moody, easy to get angry and sweated more often than before. Urine output is normal, with no complaints of chest pain, nosebleeds, gum bleeding and cough. The patient is known to have a history of hyperthyroid since 1 month ago and has been administered with Methimazole 10 mg every 8 hours and propranolol 10 mg every 8 hours. The patient has a history of COVID-19 infection twice during 2020-2021. Patient’s grandmother from the father’s side also has a history of abnormal thyroid function. The patient works as a housewife and has 1 child who is 5 years old. The patient has a history of 1 miscarriage (2016) of the first child. The patient doesn’t drink alcohol/ smoke cigarettes.

Physical examination showed patient is severely ill, with a consciousness rate of Glasgow Coma Scale (GCS) E3V5M6, blood pressure is 100/60 mmHg, heart rate of 150 times per minute, the temperature at 40 degrees celsius and respiratory rate of 24 times per minute with peripheral oxygen saturation of 99% with the help of 2 liters per minute nasal cannula oxygen administration. Physical examination of the head and neck doesn’t reveal any exophthalmos, enlarged lymphatic glands of the neck and enlarged thyroid gland. Throat examination reveals pharynx hyperemia and enlarged tonsils with crypts and detritus. Chest examination with heart and lung physical examination reveals normal findings. The abdominal examination doesn’t show any bowel sound/ organ enlargement increase. Extremities examination reveals warm acrals with no edema.

A complete blood count examination is performed and the result showed that the patient’s hemoglobin is 12.2 g/dL, MCV is 81, MCH is 27.70, hematocrit is 37.40%, leucocyte is 1.03X10^3/µL, Lymphocyte is 91.30%, thrombocyte is 190x10^3/µL and neutrophil is 0.02X10^3/µL. Blood chemistry tests showed that Serum glutamic oxaloacetic transaminase...
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mandible, parathyroid gland, colli and supraclavicle left and right (Figure 3).

Blood smear test results showed lower leucocyte count, with differential count neutropenia and relative lymphocytosis. No toxic granules or vacuolization, young cells not found, normal platelet count, giant platelet found with normal distribution. Erythrocyte seems to be hypochromic micrositer, poichylocytosis with existing ovalocyte, teardrop cell, fragmentosit and target cell, no polychromacia and normoblast found (Figure 4).

Based on anamnesis, physical examination and other supportive diagnostic examination, the patient is diagnosed with a thyroid crisis with febrile neutropenia. The patient is then administered to the ward with planning therapy of intravenous fluid of 2000 cc/24 hours, propylthiouracil (PTU) 600 mg loading dose continued by 200 mg every 8 hours per oral, 40 mg of propranolol every 8 hours per oral, 40 mg of hydrocortisone continued by 100 mg every 8 hours intravenously, 600 mg of KSR every 12 hours per oral, 2 gram of ceftriaxone every 24 hours intravenously, and 750 mg of levofloxacin every 24 hours intravenously. The patient is also planned to be consulted by the hemat-oncologic division to evaluate the cause of febrile neutropenia and the evaluation of granulocyte colony-stimulating factor (GCSF) administration after 5 days. After 5 days of treatment with granulocyte colony-stimulating factor (GCSF), a correction in complete blood count result was found, which revealed hemoglobin is 9.20 g/dL, MCV 79.70, MCH 27.10, hematocrit 27.10%, leucocyte 4.06x10³/ul, lymphocyte 49.50%, platelet 302 x 10³/ul, neutrophil 1.01x10³/uL. Due to significant improvement in the patient clinically and from the blood test result, the patient was allowed to go home on 20th July 2022 and was administered to the endocrine clinic the following days. The patient returned to the endocrine clinic on 25th July 2022 and was administered 10 mg of thiamazole every 8 hours and 40mg of propranolol every 8 hours to be taken daily. On 6th August 2022, another blood test was performed, and the result showed that hemoglobin is 10.8 g/dL, MCV 86.5, MCH 28.5, hematocrit 32.80%, leucocyte

(SGOT) is 27.8 U/L, Serum glutamic pyruvic transaminase is 35 U/L, the random blood glucose level is 95mg/dL, blood urea nitrogen (BUN) is 9.30 mg/dL, Creatin Serum is 0.6mg/dL. Blood gas analysis showed that pH is 7.44, pCO2 31mmHg, pO2 80, BE -3.1 mmol/L, HCO3 21.10 mmol/L, SO2c 96%, TCO2 22.10 mmol/L, Natrium 128 mmol/L, Kalium 3.3 mmol/L. The thyroid function test showed that FT4 is 2.37. A previous thyroid function test on 15th June 2022 showed that TSH is 0.01 uIU/mL and FT4 is 3.04mg/dL. Urinalysis examination shows pH is 6.00, leucocyte not found, nitrate not found, protein +1, ketone +1, blood not found, leucocyte sediment 2, epithelial sediment 6, erythrocyte sediment 1. A urine culture is performed and no bacterial growth is found. NS-1 antigen test is also performed to see the possibility of dengue fever, resulting in negative results. The Procalcitonin test is also done and the result is 11.31 ng/mL. When the symptoms showed up at the emergency room, Burch Wartofsky Score was calculated and the score was 70. The score came from a body temperature of 40 degrees celsius, heart rate of 150 times per minute and agitation and diarrhea that the patient experienced. Electrocardiography examination (ECG) showed sinus rhythm with P wave, rate of 143 times per minute, normal axis, no LVH and ST T changes found. (Figure 1). Chest X-ray examination showed no abnormal findings (Figure 2).

Ultrasonography examination reveals thyroiditis imaging with multiple solid nodules, isoechoc, wider than tall, ill-defined on left thyroid according to TIRADS 3 (mildly suspicious), non-suspicious lymphadenopathy on sub

Figure 4. Blood smear test.

Figure 5. Burch-Wartofsky score.1
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decreasing body weight with normal or increased appetite, (2) heat in toleration with excessive sweating, (3) palpitation, (4) tremor, (5) anxiety, (6) proximal muscle weakness, (7) alopecia, (8) increase exhaustion. Sinus tachycardia is the most common heart rhythm problem, but atrial fibrillation can also happen and is often seen in elderly patients, patients with heart valve disease and coronary artery disease. Women with thyrotoxicosis may come with the chief complaint of amenorrhea and oligomenorrhea. Men with gynecomastia are uncommon. During the physical examination, the patient seemed cachectic, with hyperthermia, diaphoresis, and anxiety. Patients might also have goiter, tachycardia or atrial fibrillation, dyspnea, abdominal pressure pain, hyperreflexia, proximal muscle weakness, tremor and gynecomastia. Patients with Graves disease often come with pretibial mix-edema, thyroid acropachy and onycholysis.

In this case, the patient is a 25 years old female with a thyroid crisis, diagnosis is based upon clinical findings which are 2 days fever history followed by a decrease in consciousness, palpitations, excessive sweating, diarrhea, vomiting and also excessive weight loss. These symptoms are caused by gene activation that increases metabolism and thermogenesis produced by thyroid hormone bound with the intranuclear receptor. An increased metabolic rate causes more oxygen and energy consumption in the body. The thyroid hormone affects the heart by permissive effect towards catecholamine. This activity causes an increase in beta receptor expression and increases heart rate, stroke volume, cardiac output and heart contractility. The thyroid hormone stimulates the respiratory center in the brain which causes increased oxygenation due to higher perfusion. In the musculoskeletal system, thyroid hormone increases the development of type II muscle fibers, which make the muscle fibers twitch quickly and contract powerfully. Thyroid hormone also increases basal metabolic rates, which cause an increase in gene expression of Na+/K+ ATPase in certain tissues that cause an increase in oxygen consumption, respiratory rate and body temperature. A

2.3x103 /uL, lymphocyte 56.30%, platelet 228x103/ul, neutrophil 0.68x103/ul.

DISCUSSION

The thyroid hormone influences the function of each organ system in the body. The thyroid hormone can increase metabolism, heart rate, and ventricle contractility and trigger muscle and central nervous system activity. Two main types of thyroid hormone are thyroxine (T4) and triiodothyronine (T3), which are excreted by the thyroid gland with a ratio of 20:1. Peripherally, T4 is changed into active T3, which is three to four times stronger than T4. Hyperthyroidism happens when there is excessive thyroid hormone due to hyperfunction of the intrinsic thyroid gland. At the same time, thyrotoxicosis refers to the overload of thyroid hormone caused by other cases (including thyroid hormone overdose). Prevalence of thyrotoxicosis in America is 1.2%, 0.5% of that 1.2% is overt thyrotoxicosis, and 0.7% is subclinical hyperthyroid. The incidence of thyrotoxicosis usually happens in the range of 20 to 50 years old. Graves disease is the most common cause, with an incident rate of 20 to 50 cases per 100,000 people, followed by multinodular toxic goiter and toxic adenoma. Graves disease is more common in women aged 30 to 50 years old with a ratio of men to women of 5:1 but it can also happen to any age in both genders. In this case, the patient is 25 years old female.

The extreme manifestation of thyrotoxicosis is called a thyroid storm. It manifests as an acute hypermetabolic, severe and life-threatening condition caused by the over release of thyroid hormone that causes adrenergic hyperactivity or peripheral response change towards thyroid hormone itself by any trigger. Patients with thyrotoxicosis come to the hospital usually with the sign and symptoms that relate to the excessive thyroid hormone, which includes: (1) decreasing body weight with normal or increased appetite, (2) heat in toleration with excessive sweating, (3) palpitation, (4) tremor, (5) anxiety, (6) proximal muscle weakness, (7) alopecia, (8) increase exhaustion. Sinus tachycardia is the most common heart rhythm problem, but atrial fibrillation can also happen and is often seen in elderly patients, patients with heart valve disease and coronary artery disease. Women with thyrotoxicosis may come with the chief complaint of amenorrhea and oligomenorrhea. Men with gynecomastia are uncommon. During the physical examination, the patient seemed cachectic, with hyperthermia, diaphoresis, and anxiety. Patients might also have goiter, tachycardia or atrial fibrillation, dyspnea, abdominal pressure pain, hyperreflexia, proximal muscle weakness, tremor and gynecomastia. Patients with Graves disease often come with pretibial mix-edema, thyroid acropachy and onycholysis.

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certain type of metabolism can also induce lipolysis or lipid synthesis, stimulate carbohydrate metabolism and protein anabolism, and induce high-dose protein catabolism. The thyroid hormone doesn't alter blood glucose levels; however, it may cause an increase in glucose reabsorption, gluconeogenesis, glycogen synthesis and glucose oxidation. Laboratory findings of the patient showed an increase in FT4 level and a decrease in TSH level, this is caused by the hypothalamus releasing thyrotropin-releasing hormone (TRH) that stimulates the secretion of TSH in the pituitary gland. Therefore an increase in T4 and T3 level, an increase in T4 and T3 levels will inhibit the release of TRH and TSH through the reverse negative loop. In addition, secretion of T3 and T4 and iodium uptake decrease. Other hormones such as somatostatin, glucocorticoid and dopamine also inhibit the production of TSH.

Cold temperature, stress and exercise may increase the release of TRH. TSH and free thyroxine (FT4) level tests are the tests of choice for early diagnosis of thyroid disease. These tests determine whether the disease appears primarily from the thyroid hormone, peripherally from hypophysis (secondary), or hypothalamus (tertiary). In suspected primary hypothyroidism, the thyroid gland inadequately releases thyroid hormone. Therefore TSH level will rise quickly while the free T4 level will be lower than normal. In primary hyperthyroidism, free T4 levels increase abnormally and TSH levels decrease quickly. Other laboratory testing such as TSH receptor antibody or peroxidase thyroid antibody can also help the diagnosis of graves disease or Hashimoto Thyroiditis.

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Free T4 levels are not required to diagnose thyroid crisis itself, but clinical manifestation that is interpreted by Burch-Wartofsky score calculation is much more important and needed to establish the diagnosis.

In this case, the patient has a low potassium level of 3.3 mmol/L. Low potassium level is the most common electrolyte imbalance problem. A potassium level of 2.5-3.0 mmol/L is considered moderate hypokalemia while a potassium level of <2.5 mmol/L is considered severe hypokalemia. This occurrence may be caused by decreased nutrition uptake and excessive potassium output through the digestive tract and kidney and may also be due to potassium shifting from extracellular to intracellular. Hypokalemia due to thyrotoxicosis is caused by increased sensitivity towards catecholamine and thyroxine that affects Na/K-ATPase activity. Hypokalemia may show several symptoms such as muscle weakness, palpitation, heart rhythm problems, polyuria, nausea and vomiting.

In this case, laboratory findings showed that the patient has leukopenia and neutropenia. Treatment of adults with neutropenia is based on his/her condition. If the patient has an acute fever and when the vital signs show an indication of sepsis, he/she should be immediately treated in the hospital, and broad-spectrum antibiotics should be administered immediately. Early treatment of neutropenia doesn't require the exact etiology of the neutropenia itself if the patient is in critical condition. After the patient is stable, treatment is continued by the algorithm of neutropenia and following disease treatment. Detailed medical history about medications and other previous laboratory tests are needed to determine how long the patient has had neutropenia. Infection history, previous hospital care due to infection, and place of previous infection (e.g. otitis, sinusitis, soft tissue infection) will also help the diagnosis. The gastric operation history must also be considered for every malnutrition or malabsorption. Decreased body weight followed by night sweating and night fever

![Figure 7](image_url)  ATD mechanism for agranulocytosis process.

![Figure 8](image_url)  Management ATD with agranulocytosis.
should also be noticed in order to eradicate the possibility of malignancy towards the existing neutropenia.\textsuperscript{13}

Severe neutropenia in patients with hyperthyroidism is very-difficult, especially in diagnostic and therapeutic management, because antithyroid drugs can’t be administered if the absolute neutrophil count is <1x10\(^9\)/L. anti thyroid drug is the most effective and considered safe for Hyperthyroidism GD, but the contraindication and bad side effects may inhibit its usage, including severe neutropenia, which is one of the most popular side effects of the antithyroid drug that may appear during the treatment of hyperthyroidism.\textsuperscript{14}

Antithyroid drug therapy is one treatment option for hyperthyroidism, followed by surgery and radioactive iodine therapy. Some drugs used are carbimazole, methimizole, thiamizole, benzylthiouracil and propylthiouracil. PTU and MMI are effective inhibitors of thyroid iodide peroxidase enzyme that catalysis biosynthetic thyroid hormone. MMI works by inhibiting peroxidase activity in the thyroid gland, suppressing triiodothyronine (T3) and thyroid (T4) synthesis. PTU works by inhibiting peroxidase and iodination of tyrosine in the thyroid gland, therefore suppressing the synthesis of T4. Meanwhile, PTU also disturbs the transformation of T4 to T3, which is at a lower free T3 level (FT3). Propylthiouracil (PTU) or carbimazole (or methimizole) can also be used, but PTU is traditionally preferred due to its rapid onset and the additional benefit of inhibition of T4 to T3 conversion which is mediated by peripheral deiodinase enzyme. PTU should be administered orally or through a nasogastric tube for the patient that doesn’t respond with 600mg of a loading dose followed by 200-250 mg regular dose every 4-6 hours. Carbimazole (or methimizole) is given at 20-30 mg every 4-6 hours.\textsuperscript{15} These antithyroid drugs are used in patients with hyperthyroidism for long term or before surgery. The antithyroid drug is often related to the incidence of neutropenia and agranulocytosis.\textsuperscript{16}

Drug-induced agranulocytosis is defined as a condition where the neutrophil count is <0.5x10\(^9\)/L with coexisting fever and/or signs of infection, (1) agranulocytosis happened during therapy or after 7 days of related drug administration and gets better (neutrophil >1.5x10\(^9\)/L) after 1 month of drug administration stopped, (2) agranulocytosis incidence may reoccur when the same drug is administered again (uncommon due to high mortality rate of such treatment), (3) agranulocytosis diagnosis can’t be taken in consideration of the patient has a history of congenital neutropenia or autoimmune neutropenia also the history of infectious disease including viral infection, history of chemotherapy or radiation and history of hematologic abnormality.\textsuperscript{17,18}

Febrile neutropenia is defined as a condition where the oral temperature is greater or equal to 101 F, or the temperature is greater or equal to 100.4 F for at least one hour, with an absolute neutrophil count less than 1500 cell/ microliter. The mechanism of ATD-induced neutropenia is still unclear. Two hypotheses are thought to be the cause of neutropenia (1) due to the toxic effect of oxidative process caused by ATD which is mediated by myeloperoxidase and cytochrome P450, creates reactive metabolites that induce direct apoptosis and through inflammation, (2) humoral autoimmune reaction happened to bone marrow stem cells (Figure 7). A genetic study showed possibilities that determine Grave disease patients that carry allele HLA DRB*08032 may be vulnerable to getting agranulocytosis after methimazole administration.\textsuperscript{1,19,20}

Agranulocytosis usually occurs in the first 3 months of ATD treatment, but some cases showed that it might start as soon as 5 days after ATD administration. The difference in onset might be due to the disease mechanism, an immune-mediated process that causes neutrophil destruction faster than the direct toxic. There is no proof that the neutropenia caused by ATD depends on the administered dose. Few types of research worldwide showed that patient with the same dose equal to or more than 30mg per day is more likely to experience neutropenia, but another research showed that ATD-induced neutropenia doesn’t depend on ATD dosing, age or treatment duration.\textsuperscript{17}

Symptoms of severe neutropenia doesn’t differ from that of severe neutropenia caused by other cause. The most common symptom is fever and sore throat. Other symptoms such as pneumonia, sepsis, anorectal infection and skin infection may also appear. Patients with severe ATD-induced neutropenia usually come with thyrotoxicosis treatment such as tachycardia, tremor, anxiety and pulsatile goiter. Febrile neutropenia treatment is done by first identifying and stopping the ATD responsible for preventing further damage. Broad-spectrum antibiotic administration given intravenously is the treatment of choice. Blood and urine cultures should be performed before antibiotics administration. Granulocyte colony-stimulating factor (GM-CSF) administration can be used in febrile neutropenia patients. GM-CSF is proven to reduce hospital care so that the patient can be administered home more quickly. In recovery, the patient will still experience acute hyperthyroidism due to ATD stoppage. Alternative medication for hyperthyroidism should be considered, which is why surgery and radioactive iodine can be an effective option to reach euthyroid conditions (Figure 8).\textsuperscript{4}

The prognosis of neutropenia induced by antithyroid drugs has increased and become better with the advancing of supportive care including antibiotic treatment, blood transfusion and the use of GM-CSF.\textsuperscript{13}

CONCLUSION

A thyroid crisis accompanied by febrile neutropenia is one of emergency. Thyroid crisis refers to the clinical findings and thyroid hormone test results. There is no specific method to predict the appearance of febrile neutropenia caused by the antithyroid drug. Frequent blood tests must be done in patients who consume antithyroid drugs. Diagnosis of drug-induced febrile neutropenia needs to be done correctly and as soon as possible so that intervention can be immediately done to reduce the mortality rate.

CONFLICT OF INTEREST

The authors declare that there is no competing interest regarding the manuscript.
ETHICAL CONSIDERATION

A subject voluntarily consented to the study’s publication, understanding that the patient’s identity would remain private. ICMJE (International Committee of Medical Journal Editors) ethics approval has been obtained.

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AUTHOR CONTRIBUTION

Commencing with the planning and ending with the report’s publication, all writers participated in this study.

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