DIAGNOSIS AND MANAGEMENT OF ANTITHYROID DRUG INDUCED AGRANULOCYTOSIS

Maulina Debbyousha[1], Hendra Zufry[2], Krishna W Sucipto[2]

[1]Registra of Endocrinology, Metabolism and Diabetes- Internal Medicine Department, School of Medicine Universitas Syiah Kuala/Dr.Zainoel Abidin General Teaching Hospital, Banda Aceh
[2]Division of Endocrinology, Metabolism and Diabetes, Department of Internal Medicine, Faculty of Medicine, Syiah Kuala University/Dr. Zainoel Abidin General Teaching Hospital, Banda Aceh

ABSTRACT

Agranulocytosis as adversed effect of antithyroid drug (ATD) in patients with Graves disease is a rare complication but it can be serious and life threatening. The mortality rate 2-10% caused by severe infection as complications. Immediate diagnosis and management are essential for proper treatment and good prognosis.

A 35-year-old female with Graves disease was complaining of fever and sore throat. She was initially treated with Thiamizole 1x20 mg for 2 weeks. Physical examination revealed leukoplakia and diffuse struma. Laboratory test : FT4 43 pmol/L, TSHs :0,005 uIu/mL, ANC <100/ul. Patient is diagnosed with ATD induced agranulocytosis. Treatment includes meropenem, fluconazole and GCSFs. The clinical and laboratory parameter improved after two weeks of treatment.

Agranulocytosis in Graves' disease patient which had ATD is a rare occurrence, with an incidence 0,2-0,5% (66,7% had severe infection). The diagnostic criteria for agranulocytosis caused by ATD are hyperthyroid patients who are confirmed with an increase T4 and/or T3, decrease in TSH, ANC of 1500/ul before receiving ATD, ANC < 500/ul after initiation ATD and other causes of agranulocytosis have been excluded. In fact, most patients had ANC <100/ul. There are no symptom difference with agranulocytosis caused by other cause. High fever and sore throat are the most common symptom. Initial management are to identify, immediately stop the drug use, broad spectrum antibiotics and GCSFs. The hyperthyroidism will continue and alternative therapies should still be given. The best prevention is to educate patient and to examine granulocyte count frequently.

I.INTRODUCTION

Antithyroid drugs are one of the main therapeutic modalities in Graves' disease, together with thyroidectomy and radioactive iodine. Antithyroid drug options include propylthiouracil (PTU), carbimazole and methimazole/thamizole. Currently, carbimazole and methimazole are more widely used because of their longer half-life, with a lower risk of side effects. One of the main side effects of PTU and methimazole is agranulocytosis, which generally occurs in the first 2-6 months of treatment and the incidence increases with greater dosing of antithyroid agents (1–4,7).

Agranulositis is a very severe state of neutropenia, where the neutrophil type count is < 500/µl. Agranulocytosis is a rare complication of treatment, occurring in 0.2-0.5% of Graves' disease patients who receiving antithyroid drugs. Agranulocytosis is serious and life-threatening, with a mortality rate of 2-10% due to severe infectious complications (2-10).

The mechanism of agranulocytosis due to antithyroid drugs is an immune-mediated process and direct toxicity. Complementary IgM antibodies are found that attack granulocytes, this immune process takes place quickly while the destruction of granulocytes due to intoxication occurs immediately after a few weeks. Acute onset in patients is characterized by symptoms of infection such as high fever and sore throat, but some patients are also asymptomatic. Furthermore, blood tests need to be performed, and the diagnosis can be made if the absolute neutrophil count (ANC) < 500/µl after receiving antithyroid drug therapy (7-9). Correct diagnosis and treatment will give a good prognosis. The best way to prevent morbidity and mortality in agranulocytosis due to antithyroid drugs is to provide appropriate education to patients (7-9).

II. CASE REPORT

A 35-year-old woman comes to the emergency department with a complaint of high fever that has been getting worse since 3 days before she was admitted to the hospital. The patient also complained of white patches in the mouth accompanied by sore throat. Previously, the patient had a history of taking the antithyroid drug thiamazole, 1x 20 mg for 2 weeks.

On physical examination, he was conscious of compos mentis, blood pressure: 90/60 mmHg, pulse rate: 100 x / min, respiratory rate: 22 x / min, temperature: 39.3^{0}C. On oral examination revealed leukoplakia on the buccal and tongue, hyperemia pharyngeal and tonsillar hypertrophy T3/T3. Diffuse goiter was palpated in the neck, no tenderness was found. Other physical examinations were within normal limits.

On laboratory examination, thyroid function values were FT4 43 pmol/L, TSHs: 0.005 µIu/mL, routine blood tests were carried out every day, with results on the first day: Hemoglobine 7.9 g/dL, Hematocrit: 24%, leukocytes 1.100/µl, platelets 475000/µL, count the type of leukocytes Eosinophils/ Basophils/ Stem neutrophils/segment neutrophils/Lymphocytes/ Monocytes : 4/1/0/0/91/4, ANC value 0. The eighth day the patient was treated: leukocytes 800/µl, count Types of leukocytes Eosinophils/ Basophils/ Rod neutrophils/ Segmented neutrophils/ Lymphocytes/ Monocytes : 5/1/0/2/87/5, ANC value of 16/µl. The twelfth day of hospitalization: leukocytes 1600/µl, leukocyte count Eosinophils/ Basophils/ Stem neutrophils/segment neutrophils/Lymphocytes/ Monocytes: 2/2/0/1/79/16, ANC value 160/µl. The thirteenth day the patient was treated: leukocytes 3200/µl, leukocyte count Eosinophils/ Basophils/ Stem neutrophils/segment neutrophils/Lymphocytes/ Monocytes : 0/1/0/43/40/16, ANC value of 1.376/µl. The fourteenth day the patient was treated: Hb 10.3 g/dL, Hematocrit: 32%, leukocytes 9400/µl, platelets 323500/µL, leukocyte count Eosinophils/ Basophils/ Stem neutrophils/segment neutrophils/Lymphocytes/ Monocytes: 0/0 /0/68/23/9, ANC value of 6.392/µl.

Morphological examination of peripheral blood revealed normochromic normocytic anemia and leukopenia. The results of routine urine examinations were within normal limits. Blood culture results: no growth of bacteria (absence of bacterial growth can also be caused by: the patient has received antibiotic therapy, the time of taking blood is not at the time of fever, the volume of blood taken is not appropriate, infection by fastidious bacteria and infection can be caused by microorganisms other than bacteria).

The patient was diagnosed with agranulocytosis caused by antithyroid drugs. The patient was treated for 14 days in an isolation room with the management of IVFD Ringer lactate 30 drops per minute, IV meropenem 1 g every 8 hours, IV Fluconazole 200 mg/24

hours, GCSFs 1 vial per 24 hour SC for 7 days, paracetamol 3x500 mg and Nystatin drop 2 ml per 6 hour. In the treatment of patients experiencing clinical improvement and improvement of laboratory parameters, which reached ANC > 1000/µL, the patient was discharged with education that he would be given a choice of other hyperthyroid therapy modalities.

III. DISCUSSION

3.1 Definition

Neutropenia was categorized into mild (ANC 1000-1500/µl), moderate (ANC 500-1000/µl), and severe (ANC < 500/µl). Drug-induced agranulocytosis was defined as absolute ANC < 500/µl, in fact most patients had ANC values < 100/µl (8-10).

3.2 Epidemiology

Agranulocytosis is estimated to occur in 0.2-0.5% of Graves' disease patients receiving antithyroid drugs. Tajiri et al who conducted a study on 15,398 patients with Graves' disease in Japan, found no difference in the incidence of agranulocytosis between patients receiving PTU and receiving methimazole. In 2% of patients receiving methimazole and 27.8% of patients receiving prophylthiouracil, 20.4% occurred in patients with Graves' disease relapse who received the same drug therapy. The median duration of antithyroid drug treatment until agranulocytosis occurred was 44 days. The mean dose of antithyroid drugs given at the onset of agranulocytosis was 23.0+10.8 mg/day for methimazole and 281.1+114.1 mg/day for prophylthiouracil (7,8,10,11,14).

In the largest study of agranulocytosis caused by antithyroid drugs involving 754 cases, the most age of onset was 28-59 years, 45% of patients experienced agranulocytosis at the age of 40-50 years, where women were more than men, namely 10.4: 1. (7,8,10,11,14).

The mortality rate from agranulocytosis is around 2-10%. Factors that worsen the prognosis include age > 65 years, pancytopenia, impaired liver function and kidney failure (15).

3.3 Pathophysiology

In general, there are two mechanisms that can explain how the occurrence of agranulocytosis caused by the use of antithyroid drugs. A number of drugs are known having the potential to oxidize neutrophils through reactive metabolites, it will cause an immune response by activating inflammation that will interfere with neutrophils with direct toxicity.

Antithyroid drug accumulation in neutrophils was found, in line with this hypothesis. This reaction is mediated by myeloperoxide which is seen earlier in granulocyte development during hematopoiesis. The oxidative process is complemented by cytochrome P450 (CYP), it explains why some drugs can cause neutropenia or agranulocytosis and can also cause liver toxicity. Immune mechanisms also have a role in pathogenesis. Circulating antibodies against granulocyte differentiation play a role in PTU-induced agranulocytosis, immune mediation contributing to this process. These antibodies include anti-neutrophil cytoplasmic antibodies (ANCA), which act against specific granules within neutrophils when they migrate to the cell membrane, triggering apoptosis. These antibodies can also react with myeloid progenitor cells and trigger opsonization of neutrophils, mediated by the complement system. Chen et al identified the genetic background of drug side effects, They found that human leukocyte antigen (HLA)-B*38:02 and HLADRB1*08:03 were both associated with genotyping and genomewide. Furthermore, Cheung et al. found that HLA-B*380201 was closely associated with carbimazole/methimazole-induced agranulocytosis, but not propylthiouracil (PTU). This allele is more prevalent in Asian than European populations (7,13).

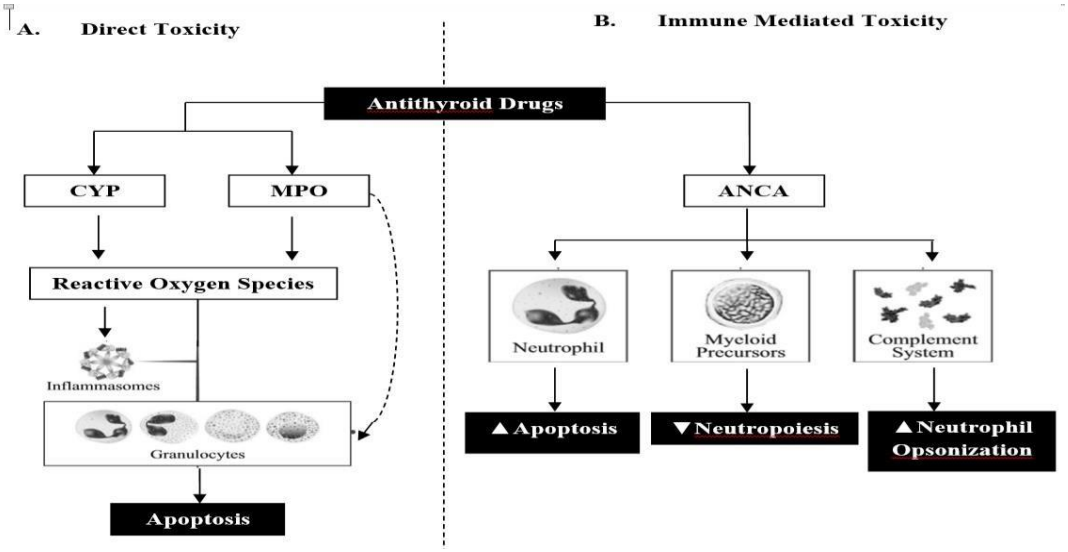

Figure 1. Pathophysiology of agranulocytosis caused by antithyroid drugs

3.4 Clinical Manifestations

Agranulocytosis usually occurs after the first 3 months of antithyroid drug administration, but cases after 5 days of antithyroid drug use up to more than 10 years are also found. This difference in onset time is related to the mechanism of the disease, and to an immune-mediated process that causes neutrophil destruction. The average duration of use of

propylthiouracil (PTU), carbimazole and methimazole to cause agranulocytosis was 36, 41 and 42 days (6,7,10,12,13).

The symptoms of agranulocytosis caused by antithyroid drugs are no different from agranulocytosis caused by other causes. High fever (92%) and sore throat (85%) were the most common complaints. Acute pharyngitis (46%), acute tonsillitis (38%) gingivitis, oral ulcers, other infections of the oral cavity, muscle aches, severe pneumonia (15%), urinary tract infections (8%) and anorectal or skin infections are other clinical manifestations that also often found. Sepsis should be considered especially if the patient has fever and chills that appear suddenly. 15% of patients were asymptomatic. Patients with agranulocytosis induced by antithyroid drugs may also present with symptoms associated with a thyrotoxicotic condition (tachycardia, tremor, anxiety and goiter) (2,7,12).

Pancytopenia was found in 1.2% of patients with agranulocytosis due to antithyroid drugs. Hemopoetic damage can be found in patients without any clinical manifestations, so it is necessary to consider a complete count examination after 2 weeks of taking anti-thyroid drugs (6,12,14,15).

3.5 Diagnosis

The diagnosis is made when ANC < 500/µl is obtained with clinical manifestations as mentioned above. Bone marrow examination is considered to rule out malignancy, determine cellularity and to determine myeloid maturity. Bone marrow imaging reveals selective reduction or absence of granulocytic precursors with normal or increased erythropoiesis, proliferating megakaryocytes or left shifting of granulopoiesis with few or no mature granulocytes (14,15). The diagnostic criteria for agranulocytosis caused by antithyroid drugs are:

(1) The patient is a confirmed hyperthyroid patient with an increase in plasma T4 and/or T3 accompanied by a decrease in the concentration of TSH
(2) Patients confirmed to have a granulocyte count of 1500/µl before receiving antithyroid drugs
(3) The granulocyte count decreased below 500/µl after initiation of antitrioid drug therapy, and agranulocytosis improved after the antithyroid drug was discontinued.
(4) Other causes of agranulocytosis have been excluded

Resolution of agranulocytosis induced by antithyroid drugs is when the granulocyte count is > 1000/µL (14).

The study of Cheung CL et al used single nucleotide polymorphisms (SPNs) to study antithyroid drug-induced agranulocytosis in an ethnic Chinese population. The results showed the HLA-B*38:02:01 variant as the appropriate locus for agranulocytosis. The Hallberg study used SPNs to determine patterns of genetic variation associated with agranulocytosis in European populations. The results identified three genetic variations associated with antithyroid drug-induced agranulocytosis: rs652888 located in the EHMT2 intron, HLA-B*27:05 and HLA-B*08:01. The predictive ability of the three variants is high.(17)

3.6 Treatments

Initial management is proper identification and immediate discontinuation of the drug to prevent further damage. Intravenous broad-spectrum antibiotics are the mainstay of therapy, initiated immediately after blood, urine and culture studies. Antifungal therapy, as well as other supportive therapy such as parenteral fluids are also required. Hospitalization is needed to monitor disease progression and administer intravenous drugs. Examination and prevention of infection is needed, including maintaining good hygiene in high-risk areas such as the mouth, skin and perineum. The median time between the onset of acute agranulocytosis and normalization of the ANC after the use of PTU, carbimazole and methimazole was 10 days, 8 days and 10 days (7-10).

Haemopoetic growth factors such as granulocyte-colony stimulating factor (GCSFs) can be used in agranulocytosis caused by the use of antithyroid drugs. The use of GCSFs has been shown to reduce the time required for hematological recovery, duration of antibiotic use, length of stay and cost efficiency. It takes about 5 days to 2 weeks for neutrophil recovery (7,10).

During the recovery from agranulocytosis, the patient will continue to have hyperthyroidism. Alternative therapies to treat hyperthyroidism should still be given. Surgery and radioactive iodine are reasonable options, with 88.8% of patients achieving euthyroid after treatment (7).

Radioactive iodine is an option in patients at high risk for surgery. Contraindications are pregnancy, lactation, coexistence with thyroid cancer, active exophthalmos, and large goiter. Surgery is an option in patients who have large goiter. Contraindications are comorbidities that will increase the risk of surgery, late-stage cancer, and the absence of an experienced surgeon. The recommended surgical procedure is a total thyroidectomy which aims to prevent recurrence of Graves' disease. The most common complications are hypoparathyroidism, laryngeal nerve injury, and postoperative bleeding. Treatment given

before surgery is the administration of beta blockers and glucocorticoids. Beta blockers are symptomatic therapy that control the symptoms of hyperthyroidism, reduce the effects of thyroid hormones in the periphery, while glucocorticoids inhibit the conversion of T4 to T3. In hyperthyroid conditions that are not controlled by giving beta-blockers and glucocorticoids, lithium carbonate 1200 mg/day can be given, lithium carbonate can reduce thyroid hormone levels. Another alternative is cholesterol, a drug commonly used in dyslipidemia. Cholesterol affects the absorption of thyroid hormone, increasing its excretion via the faeces and decreasing its concentration in serum. Lugol's solution is given perioperatively 7-10 days before surgery, aiming to reduce the vascularity of the thyroid gland.(15)

3.7 Prevention

The onset of agranulocytosis caused by antithyroid drugs can occur suddenly, even in one case, clinical manifestations are found in normal ANC, this is the basis for periodic routine examinations, even though financially it becomes ineffective. Tajiri et al reported that this method is the best way to find asymptomatic patients. Examination of the granulocyte count at each visit showed an accurate diagnosis in 64% of patients with agranulocytosis or and 94% in asymptomatic granulocytopenia.(5,7,16,17) .

In Japan, on the use of methimazole (MMI) and propylthiouracil (PTU) it is recommended that blood counts be checked every 2 weeks in the first 2 months of treatment or concurrently with thyroid hormone evaluation, and if the granulocyte count <1000/uL, even if asymptomatic, the patient is consulted to the hospital. doctor for further examination (16).

The best prevention is to educate patients when prescribing antithyroid drugs. Robinson et al reported that 60.9% of patients were not aware of the symptoms of agranulocytosis and 30% of these patients after investigation, found the fact that patients did not receive an explanation of agranulocytosis so that they experienced delays in diagnosis which could result in an increased risk of mortality (6,17,18).

IV. Conclusion

In clinical practitioner's perspective, agranulocytosis as a serious side effect should be considered in patients prescribed antithyroid drugs, especially in patients who complain of high fever and other symptoms of infection. From the patient's perspective, medical help should be given immediately after getting the initial symptoms, ANC < 500/µl is an important diagnostic value and needs to be treated immediately. A complete and good education when giving antithyroid drugs to patients is very important and should be considered in a structured program. The development of knowledge about the genetic background in this case is important

for the future in identifying populations that have a high tendency to experience agranulocytosis, so that more stringent granulocyte examinations can be carried out in these patients and other modalities of hyperthyroid therapy are considered.

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