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ANTITHYROID DRUG – INDUCED AGRANULOCITOSYS – A CASE SERIES

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Abstract: **Antithyroid drugs (ATDs) are a large group of medications that act on the metabolism of the thyroid hormones. They are associated with various side effects such as toxic hepatitis and leukopenia. We report two patients hospitalized at "Mother Teresa" University Hospital Centre in Tirana, Albania as Leukopenia from ATDs. Both patients were middle aged women, in treatment with ATDs that showed signs of fever, sore throat and mild muscular pain during their first examination. In their blood test resulted low white blood cells level and agranulocytosis. They were not taking other medication nor did they have other diseases. Excluding other confounding factors by differential diagnosis, it was concluded that it was their long treatment with ATDs the reason of Leukopenia. Interruption of the drug and close follow up were needed. In conclusion, ATDs were linked with serious side effects which should be considered in every patient with hyperthyroidism treated with this class of drugs.**

Keywords: **Antithyroid Drugs – Hyperthyroidism – Agranulocytosis – Fever – Differential Diagnosis.**

1. INTRODUCTION

Hyperthyroidism is a group of symptoms that results from the increased levels of thyroid hormones in the blood. It can be a clinical manifestation of autoimmune, infectious diseases or malignancy of the thyroid gland. Depending on the cause, one of the chosen treatments are antithyroid drugs (ATDs). ATDs include a wide range of drugs that act centrally and peripherally on the metabolism of the thyroid hormones. They are associated with a number of side effects. Among the more serious effects are toxic hepatitis and leukopenia. In a meta-analysis of 2017, leukopenia by ATD in Graves' Disease only occurs in 0.2 - 0.5% of patients with the highest predominance in female sex and the population over 40 years.[1, 2]

ATDs act directly or by mediating immunity on granulocytes displaying toxicity especially to neutrophils.[3]

Although the cellular effect of ATDS begins rapidly, the shown effect on peripheral blood delays from 2 weeks to several months. As the blood white cell level decreases, the clinic manifestations become more prominent and the risk of mild infections to septicaemiaor even death increases. Mortality is up to 10 %. [4] For this reason, worldwide guidelines include evaluation of blood formula and hepatic function before starting and during the therapy with ATDs. If hematopoietic disfunction is noted, a prompt intervention should be instituted, including immediate discontinuation of ATDS, initiation of prophylactic immune-defence therapy, stimulation of the blood white line (if necessary), symptomatic treatment of hyperthyroidism and finding alternative methods for further treatment of the pathology of the thyroid.[5]

Assessing the importance of this effect of ATDs, we present two clinical cases hospitalized at "Mother Teresa" University Hospital Centre in Tirana, Albania as Leukopenia from ATDs.

2. CASE REPORTS

The first case is that of a woman of 64 years from Tirana presented to the Emergency Room in February 2019 with complaints of fever, high temperature, sore throat and generalized weakness.

She was diagnosed with Hyperthyroidism/ Multinodular goitre 17 years ago, treated intermittently with ATDs (Propyl thiouracil [PTU] 3x2 tb). During treatment with PTU, she recalls a hospitalization in Haematology Department with the same symptoms and blood problems she appears to have now. Unfortunately, she does not possess any documentation about this episode but from that moment the doctors stopped her PTU. In 2017 the patient stopped going to the doctor

and interrupted all medications. In December 2018, she restarted seeing the doctor because of symptoms of hyperthyroidism. Her hormone levels were: Thyroid Stimulating Hormone (TSH) 0.015 uUI/ml and free Thyrotoxin (fT4) 2.91. At that point she was given treatment with Unimazole20 mg daily. She does not recall if her blood level was checked prior to the ATDs.

At the Emergency Room, her blood sample showed a level of white blood cells (WBC) of 1000/ mm3 and Granulocytes of 12.6%.

The patient was also being treated for Arterial Hypertension and Chronic Atrial Fibrillation with Losartan, Hydrochlorothiazide, Verapamil and Xarelto.

She had a positive family history for pathology of the thyroid gland. Her daughter was diagnosed with multinodular goitre.

During physical examination her vital signs: temperature 37.5 °C, irregular pulse 94/minute, respiration rate 20/ minute, blood pressure 140 / 60 mmHg lying. She appeared to be a generally well developed, slightly obese woman in active position. She was fully oriented in space and time. No neurological deficiency. Pupils round, reactive to the light. Her face was slightly hyperaemic. Pharynx hyperaemic and mildly exudative. No adenopathy presents. Her thyroid was visible and painless to touch. Lungs with vesicular respiration. No heart murmurs present. Abdomen soft, flat, bowel sounds present. Extremities: skin warm, no oedema present. No clubbing nor cyanosis.

After consulting with the Haematologist and Infectious Disease Specialist, the patient is hospitalized in the Endocrinology Department as Leukopenia / Agranulocytosis by Unimazole.

Treatment with ATDs is immediately discontinued and prophylactic Antibiotics, Antiviral and Antimycotic therapy is started. Also, therapy with Filgrastim for white blood cell stimulation is requested.

The patient is scheduled for a myelogram and leukocyte immunophenotype analyse in order to better differentiate the diagnose but she refuses the procedure.

During the hospital stay, the analyses were as followed (as shown in table 1):

Table 1. Blood results in case 1

February, 23th (2 days prior to hospitalisation)	
White blood Cells	1100 / mm3
Granulocytes	200 / mm3 (11 %)
Haemoglobin	10.2 g/dl
Red Blood Cells	3840000/ mm3
Platelets	295000 / mm3
February, 25th (hospitalisation day)	
White blood Cells	1000 / mm3
Granulocytes	100 / mm3 (8.4 %)
Haemoglobin	9.5 g/dl
Red Blood Cells	3560000/ mm3
Platelets	298000 / mm3
February, 28th	
White blood Cells	1000 / mm3
Granulocytes	500 / mm3 (39 %)
Haemoglobin	10.6 g/dl
Red Blood Cells	3990000/ mm3
Platelets	407000 / mm3
March, 2th	
White blood Cells	1900 / mm3
Granulocytes	1300 / mm3 (69.1 %)
Haemoglobin	10.2 g/dl
Red Blood Cells	3630000/ mm3

Platelets	439000 / mm3
March, 3th	
White blood Cells	3700 / mm3
Granulocytes	2700 / mm3 (69.1 %)
Haemoglobin	11.2 g/dl
Red Blood Cells	4180000/ mm3
Platelets	463000 / mm3
March, 4th	
White blood Cells	5700 / mm3
Granulocytes	4800 / mm3 (82 %)
Haemoglobin	11.3 g/dl
Red Blood Cells	4110000/ mm3
Platelets	446000 / mm3

Other blood analyses were normal. The patient was hospitalized for a week. During this time, the blood profile was gradually coming within normal ranges.

TSH after discontinuation of ATDs was less than 0.004 uUI/ml. that is why the patient was scheduled for treatment with radioactive iodine (J^{131}). One month after the discharge, she received a dose of 8 mci J^{131}.

Months after treatment with iodine, the patient is euthyroid and with normal blood profile.

The second case we report is one of a 49-year-old female presented at the emergency room following a 4-weeks history of general weakness, fatigue, high bodytemperature and painful throat.

One month ago, she was diagnosed with multinodular goitre and she has been in treatment with Unimazol 5mg twice a day.

Clinically, the patient was a medium-framed woman, febrile with a low-pitched voice. Her blood pressure was 110/70 mmHg, she had a regular pulse of 70–90 beats per minute. Respiratory and abdominal examinations were unremarkable.

During laboratory tests, pancytopenia was observed. Blood report was: White Blood Cells (WBC) 1.4 x 10^3/mm3, Hb 10.4 g/dl, lymphocytes (LYM) 88% and granulocytes (GRA) 5.7%. Thyroid function tests showed abnormally high concentration of free T4 = 20.01 pg/ml and free T3 = 4.41pg/ml meanwhile Thyroid-stimulating hormone (TSH) was 0.681 UI/ml. The patient was then admitted to the Endocrinology and Metabolic Diseases Department for further evaluation and treatment. The patient was treated with Filgrastim 300 mcg daily; Prednisolone 25 mg, twice a day; Cefazolin 1.0 gr, three times a day and Levofloxacin 500 mg once a day.

The ultrasound of the neck showed an isoechoic nodule on the left lobe of the thyroid with microcalcifications, measuring 0.5 cm and two isoechoic nodules measuring 0.6 cm and 0.7 cm on the right lobe, normal isthmus. Abdominal ultrasonogram showed steatosis of the liver, but no other abnormal findings.

Thyroid scan (Tc99m) noted no enlargement of the thyroid gland but some hyper fixation areas in nodular shape in the lower part of the left lobe.

A bone marrow biopsy was performed. It showed predominance of lymphocytes with no other abnormalities.

Leukocyte immunophenotyping of the bone marrow was inconclusive in identifying any pathological leucocyte populations.
The lymphoid population made up 70% of all cells. A marked decrease in the granulocyte series was observed.

During treatment, ameliorations were seen, as shown in table 2.

Table 2. Blood results in case 2

	Before the treatment	One week after treatment	Seven weeks after the treatment
White blood Cells	1.4 x 10^3/mm3	13.1 x 10^3/mm3	4.92 x 10^3/mm3
Granulocytes	5.7%	71.1%	62.8%
Lymphocytes	88%	23.2%	32.7%
Haemoglobin	10.4 g\dl	10.5 g\dl	11.6 g\dl

3. DISCUSSION

ATDs have adverse hematological effects ranging from mild leucopenia to agranulocytosis and aplastic anemia. The incidence of ATD-induced agranulocytosis in patients with hyperthyroidism is rare, approximately at 0.1–1.0%. [6]

Both of our cases were females, at age 40 to 60 years old, in accordance with the epidemiological trend. In one of the largest studies regarding ATDs induced agranulocytosis was seen that the mean age of onset was 43.4 ± 15.2 years, and more affected were females. [7]

ATD-induced agranulocytosis usually occurs within 2 or 3 months of ATD treatment as reported by Tajiri et al. [8] This was seen in our cases too.

The main clinical features included flu-like symptoms, upper respiratory tract infection, high fever and general malaise. It was observed predominantly leucopenia and agranulocytosis.

Drug-induced agranulocytosis had been defined as absolute neutrophil count (ANC) less than 500/μl of blood. [9]

Differential diagnosis was made in collaboration with a hematology specialist in order to determine the origin of agranulocytosis and to exclude other potential causes such as other medication toxicity or pre existing blood malignancy.

In order to do so, many factors were considered. Firstly, medical history was the key in suspecting this possible adverse effect. The onset of clinical manifestations was usually some weeks to month after starting ATDs. Checking the blood before and during the treatment helped the differential diagnosis, as suggested in European and American guidelines.[10, 11] Then, patients were observed after hospital admission and rapid amelioration was evident. Approximately, the mean time of recuperation is 10 days, helped by treatment with granulocyte-colony stimulation factors (G-CSFs) like Filgrastim, antibiotics, antivirals and antimycotic drugs. [12] Although not all studies support the idea that G-CSFs are necessaire, in our cases their effect was positive and therefore they are being used as a first line treatment, especially in severe agranulocytosis. [13]

Lastly, bone marrow examination was studied important in evaluating myeloid maturation and any abnormal specter of cellularity. In ATDs induced agranulocytosis is frequent observing granulocytes reduction with generally normal erythropoiesis and megakaryocyte proliferation or left-shifted granulopoiesis. [14] Unfortunately this test was not performed or was inconclusive in our cases.

In patients who were diagnosed with an adverse effect of ATDs, the continuation of these drugs is forbidden and other options are considered like surgery or radioactive iodine treatment as suggested by recent guidelines. [10, 11] Although, some studies suggest that you can change the type of ATDs, cross reactions are wildly known and equally dangerous so we suggest more definite ways of treatment. [15]

4. CONCLUSION

In conclusion, ATD-induced agranulocytosis is a rare but dangerous adverse effect of the treatment. In order to prevent it, we should inform the patient of the common symptoms of agranulocytosis and conduct a routine complete blood cell count before, during and after the treatment with ATDs.

In case that agranulocytosis happens, it is important to stop the possible causative drug, confirm the diagnose while excluding other potential causes, initiate the treatment with antibiotics and granulocyte-colony stimulation factor and closely follow up the patient.

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