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Twice developed thyreostatic-induced agranulocytosis in a young patient with Graves' disease

The study is a case history of a patient with a long history of Graves' disease treated with thyreostatics in whom agranulocytosis returned (developed twice). A patient B.K., born in 1972, a psychologist, was treated for hyperthyroidism in the course of Graves' disease. The anamnesis about the course of disease from 1994 to 1999 was obtained only from the patient herself, because she was treated in another health centre and did not have any results from laboratory tests regarding the beginning of her disease. For the first two years she was administered metizol (tiamazol) without any side-effects, and then the disease was in remission for one year and the patient was not treated. Next there was a recurrence of hyperthyroidism and metizol was administered again but allergy developed (itching of the skin, allergic rash).

The patient presented at Endocrinology Clinic in August 1999. Laboratory tests revealed hyperthyroidism with high levels of antithyroid antibodies anti-TG and anti-TPO. Physical examination revealed tachycardia, profuse perspiration, slightly enlarged goitre with vascular murmur and slight exophthalmos without symptoms of inflammation. The thyroid gland on palpation and USG examination did not reveal any focal lesions. The patient was administered Metylthiouracil and Propranolol. When she presented in September 1999 she was already pregnant and symptoms of allergy to Metylthiouracil appeared. Therefore thyreostatic was exchanged for Propylthiomacil, first in small doses (50 mg/24 h), which were gradually increased as pregnancy developed, to obtain euthyreosis with higher doses (300 mg/24 h). The drug was tolerated well and no complications were observed. She delivered the baby with the birth weight 3060 g in her 39th week of gestation (April 2000). The infant was born with the symptoms of intrauterine inflammation and thrombocytopenia. TSH culture was normal. Until the present moment the development of the child is normal.

Two months after the delivery the patient developed hyperthyroidism again in spite of continuous administration of Propycil in the doses of 100 mg/24 h. The dose of Propycil was increased and euthyreosis was obtained after 6 weeks. The treatment with radioactive iodine was offered to the patient but she refused because of a health hazard for her young child. Propycil was continued but when she stopped lactating Metizol was started and there were no symptoms of allergy or drug intolerance.

In August 2002 she became pregnant again. As the increased activity of the thyroid gland remained, she continued maintenance doses of Propycil and remained in euthyreosis throughout her second pregnancy. The course of pregnancy was complicated by vaginal bleeding in the 5th–6th week of gestation (she was administered Duphaston). In April 2003, being in euthyreosis, she delivered a baby by a caesarean section for obstetric indications. At that time she was taking Propycil in a dose of 50 mg every second day. One month after the second delivery, still lactating, she developed symptoms of hyperthyroidism requiring increasing the dose of Propycil to 100 mg/24 h for a week, then to 50 mg/24 h (1 tablet).

At the beginning of July 2003, while taking Propycil in a dose of 50 mg/24h, she developed agranulocytosis with purulent angina. Blood tests revealed leukocytes – 1.2 K/ μL, neutrophils – 12%, hemoglobin – 9.6 g/dl, erythrocytes – 3,550,000, and decreased level of iron and low TSH with normal total thyroxin. The patient was admitted to the Internal Diseases Hospital and treated in an aseptic single room. She was administered broad-spectrum antibiotics: Neupogen, Encorton, Hemofer. The improvement in her blood tests with the increase in the granulocyte count up to 18% was observed after two days of treatment, and a full improvement in the blood tests was obtained after seven days of treatment (leukocytes – 6,300, granulocytes – 62%).

After this episode of severe hematologic drug-induced side-effects the patient was offered a preparation for euthyreosis with lithium carbonate and immediate total strumectomy. The patient did not follow the offered treatment and started the next course of treatment for her hyperthyroidism in another health centre where she was administered Tyrozol.

She developed granulocytosis for the second time in October 2005 while taking Tyrozol in a dose of 5 mg/24 h. She was admitted again to the Internal Diseases Hospital in severe general condition, with massive purulent and ulcerative lesions in her mouth and tonsils and temperature 40°C. Her blood tests revealed: leukocytes 0.84 K/μL, granulocytes 0.02 K/μL (1.8%), Hb – 11.9 g/dl, erythrocytes – 4,150,000, free thyroxin – 24.84 pmol/l (normal level 9–20). She was placed on a sanitary regime and the treatment was started with Neupogen, antibiotics, Encorton, local treatment of lesions in the mouth (with the solution of iodine with glycerin which had antiseptic effect and inhibitory effect on hyperthyroidism). Despite the intensive treatment and a consultation with a hematologist no significant improvement in the blood tests was obtained. Purulent lesions decreased to small patches, temperature decreased, the function of the thyroid gland returned to normal but the results of blood tests were still abnormal: leukocytes 2.03 K/μL, granulocytes – 0.8%. The patient was transferred to the Hematology Hospital where the treatment was continued with Neuprogen, Granocyte, Encorton and antibiotics. Myelography was performed: quite abundant cells of medium size in bone marrow, red blood cells stimulated constitute 49% of the total, regeneration of normoblasts, single megaloidal forms. Impaired granulocyte pattern – 22%, mainly in the form of myelocytes, single rod neutrophils and segments. In the preparation numerous megacaryocytes and platelet aggregates.

The patient was discharged home after a week of hospital stay in the Hematology Hospital. She was treated in hospital for the second agranulocytosis for 16 days altogether. On discharge her blood tests revealed: leukocytes – 4,000, granulocytes 1.38 K/μL (34.3%). The patient was prescribed Granocyte preparations as a follow-up treatment for 2 days.

She presented for a check-up at the hematologist a month after the discharge but she did not have her recent blood tests done, as ordered by the doctor. She did not present at Endocrinology Clinic either, so we have no information about her present condition neither from the hematologist nor the endocrinologist.

After the analysis of the course of the disease of the patient B.K. several important aspects from the point of view of medical practice should be considered. It should be noted that the course of the second agranulocytosis was longer and more severe in comparison with the first agranulocytosis. The response of bone marrow to the agent stimulating granulocytosis was much weaker in the second event, therefore the prognosis about her further condition was rather unfavourable.

A critical moment in this case history was prescribing a thyreostatic by a doctor, despite previous drug-induced agranulocytosis. It is clear that each of the drugs from the two groups of thyreostatics – both derivatives of thiourea (Propycil, Metylthiouracil) and of imidazol (Metizol, Tyrozol) may cause agranulocytosis and the immune response to different groups of antithyroid drugs may be similar. Therefore the previous incidence of this complication in any patient is an absolute contraindication for the administration of a thyreostatic from any of these groups in a particular patient in the future (2, 3, 6).

This rule of thumb in endocrinology was disregarded in this case, resulting in dramatically severe course of the drug-induced damage to the bone marrow. According to many authors side-effects after thyreostatics appear most often after high doses of drugs and they occur in the first three months of treatment (9). In the presented case history side-effects were revealed after several years of administration of thyreostatics when they were well tolerated and, apart from that, when minimum maintenance doses of the drug were taken (at the first and second onset of the disease).

As it is stressed by Burch (3), a routine check-up of leucocytosis may help to predict this complication only to a small degree. Toxic damage to the bone marrow develops rapidly and is the result of autoimmune oversensitivity to the administered drug (9). Lewiński emphasizes the suppressive effect of thyreostatics on granulocytopoiesis in bone marrow (5). Agranulocytosis after antithyroid drugs is a rare complication and refers to 0.2% of the treated patients (4). Even less infrequent but serious complication after thyreostatics may be drug-induced aplastic anaemia (7).

Drugs of choice in the treatment of hematologic complications after the administration of thyreostatics are the agents stimulating the increase in granulocytes G-CSF (drugs Neupogen, Granocyt). Steroid hormones are administered as a complement to the therapy in order to speed up maturation of granulocytes and their transport to the peripheral blood (8). As it is difficult to predict the incidence of drug-induced agranulocytosis in the course of treatment of hyperthyroidism, the patient should be informed about the necessity to report at the doctor immediately when a sore throat and fever appear (they may be the first symptoms of agranulocytosis) (2).

It is also important that the patient be treated by one endocrinologist who will be able to observe the patient over a long time and the course of his disease, as well as his response to the administered drugs. Such wide information will help the doctor to offer the best choice of treatment tailored to this particular patient.

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SUMMARY

The study presents a case history of a young patient, treated with thyreostatics for long lasting Graves' disease, who developed agranulocytosis twice. Symptoms and the course of treatment are described as well as the problem of drug-induced damage to the bone marrow in the course of hyperthyroidism.

Dwukrotna agranulocytoza po tyreostatykach u młodej pacjentki z chorobą Gravesa–Basedowa

Przedstawiono przypadek młodej pacjentki z wieloletnim przebiegiem choroby Gravesa–Basedowa leczonej tyreostatykami, u której dwukrotnie wystąpiła agranulocytoza. Opisano objawy oraz proces leczenia chorej. Przedstawiono problem polekowego uszkodzenia szpiku kostnego w przebiegu nadczynności tarczycy.