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Agranulocytosis during treatment of chronic hepatitis C complicated by hyperthyreosis. Case reports

Ostra agranulocytoza w przebiegu leczenia przewlekłego zapalenia wątroby typu C powikłanego nadczynnością tarczycy. Opisy przypadków

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Abstract

Agranulocytosis is a life-threatening disorder characterised by a greatly decreased number of circulating neutrophils below 500/μL. This article presents two cases of agranulocytosis in patients treated with pegylated interferon and ribavirin due to chronic hepatitis C. Interferon induced hyperthyroidism, which required the use of a tyreostatic. Anti-thyroid drugs (ATD) used to treat hyperthyroidism can cause agranulocytosis. The synergistic reaction of ATD and interferon on bone marrow cannot be excluded. **(Pol J Endocrinol 2012; 63 (1): 52–55)**

Key words: *hyperthyroidism, agranulocytosis, anti-thyroid drugs, pegylated interferon alpha, granulocyte colony-stimulating factor*

Streszczenie

Agranulocytoza jest stanem bezpośredniego zagrożenia życia rozpoznawanym, gdy liczba granulocytów obojętnochłonnych jest niższa niż 500/μl. Przedstawiono dwa przypadki ostrej agranulocytozy, która wystąpiła u pacjentów leczonych pegylowanym interferonem i rybawiryną z powodu przewlekłego zapalenia wątroby typu C. Interferon spowodował nadczynność tarczycy wymagającą zastosowania tyreostatyku. Tyreostatyki stosowane w leczeniu nadczynności tarczycy mogą być przyczyną agranulocytozy. Nie można wykluczyć ich synergistycznego działania z interferonem na szpik kostny. **(Endokrynol Pol 2012; 63 (1): 52–55)**

Słowa kluczowe: *nadczynność tarczycy, agranulocytoza, tyreostatyki, pegylowany interferon alfa, czynnik wzrostu kolonii granulocytarnych*

Introduction

Acute agranulocytosis is a life-threatening condition diagnosed when the number of neutrophilic granulocytes is lower than 500/μl. The condition is most often caused by medications, viral infections, chemotherapy, radiotherapy, autoimmune diseases, and bone marrow aplasia [1]. The cause of drug-induced agranulocytosis is the oversensitivity of bone marrow stem cells to some substances (idiosyncrasy) [2]. The clinical picture of acute agranulocytosis is most commonly characterised by fever, deterioration in general health status, and severe oral mucosal ulceration quite often accompanied by bacterial, viral, fungal superinfection. The symptoms usually subside 5–10 days after withdrawal of the agranulocytosis-inducing drug [3].

This study presents two cases of acute agranulocytosis which occurred in patients with chronic hepatitis C treated with pegylated interferon (PegIFN) and ribavirin (RBV). In both cases, the interferon therapy was complicated by hyperthyreosis which required the use of an anti-thyroid drug. The aim of the study is to draw attention to the possible occurrence of the complication, and the necessity of cooperation between specialists in several medical fields, such as hepatologists, endocrinologists, and haematologists.

Case reports

Case no. 1

Female patient K.M., aged 27, chronically infected with genotype 1 HCV, was treated with pegylated interferon alpha 2a (PegIFN alpha 2a) at a dose of 180 μg once weekly and ribavirin at a dose of 1.0 g/day. Before the treatment, the HCV RNA value was 9.34×10^4 IU/ml and the TSH level was 2.8uIU/ml [normal (N): 0.25–5.0 uIU/ml]. The initial period of treatment proceeded without complications. Haematology results were within normal limits and the HCV viremia assessed in the fourth and 12th week of treatment was undetectable. In the 12th week of treatment, the patient reported epistaxis, cold symptoms without fever. Haematology test showed a decrease in the number of platelets to 72×10^3/μl. The dose of PegIFN alpha

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Table I. *The results of selected laboratory blood tests — case no. 1*
Tabela I. *Wyniki wybranych badań laboratoryjnych krwi — przypadek nr 1*

Laboratory results (normal values)	First day of hospitalisation	Second day of hospitalisation	Third day of hospitalisation (last day)
Hb (12–16 g/dL)	11.7	11.8	11.8
Platelets (140–440 × $10^3/\mu$L)	108	112	120
Leukocytes (4–10 × $10^3/\mu$L)	1.2	3.4	5.8
Bands (3–5%)	1	15	19
Segments (57–65%)	8	30	31
Lymphocytes (20–40%)	63	44	40
Monocytes (4–8%)	28	11	10
Eosinophils (2–4%)	0	0	0
Basophils (0–1%)	0	0	0
ANC (1800–8000/μL)	108	1530	2900
CRP (0–5 mg/dL)	5.0		
PCT (<0.5 ng/mL)	<0.5		

Hb — haemoglobin; ANC — absolute neutrophil count; CRP — C-reactive protein; PCT — procalcitonin

2a was reduced to 135 μg. The subsequent haematology panels performed weekly showed an increase in the number of platelets (122 × $10^3/\mu$l). However, leucopenia and granulocytopenia occurred (leukocytes — 2.1 × $10^3/\mu$l, the absolute neutrophil count — ANC — 714/μl). The reduced dose of PegIFN alpha 2a was maintained. According to the applicable standards, in the 12th week of treatment, the TSH and thyroid hormones levels were determined and were: a decreased TSH level < 0.005 uIU/ml and thyroid hormones levels within normal limits: fT3 — 2.8 pg/ml (N: 2.60–5.40 pg/ml), fT4 — 0.97ng/ml (N: 0.69–1.55 ng/ml). Anti-TSH receptor antibody was negative. Thyroid sonography showed homogenous echogenicity and normal volume of both thyroid lobes, and no tumours were found.

In the 18th week of therapy, the full dose of interferon was reintroduced due to the satisfactory haematology result, and a week later treatment with an anti-thyroid drug began. Thiamazole was administered at a dose of 20 mg /day. Because of the drug intolerance (pain in the joints) after several days it was replaced by propylthiouracil at a dose of 50 mg /day. After six weeks of treatment, the patient was admitted to hospital because of fever, chills, severe sore throat and general weakness of one week's duration. Physical examination showed fever of 38.5°C, skin paleness, and white fur on the deep red, swollen oral and tonsillar mucosa. Blood cultures and pharyngeal swabs were taken. The results of selected laboratory tests done during hospitalisation are presented in Table I. All medications were stopped. There was administered ciprofloxacin at a dose of 2 × 200 mg intravenously (*i.v.*) and fluconazole 1 × 200 mg orally. Due to agranulocytosis, the patient received granulocyte colony-stimulating factor G-CSF (Neupogen) at a dose of 480 μg subcutaneously (s.c.). On the second day of hospitalization, the patient felt better, she did not have fever and the local pharyngeal lesions were less severe. On the following days, the pharyngeal and tonsillar lesions disappeared, and the physical condition of the patient improved. The pharyngeal swabs and blood cultures were negative. There were determined: TSH — 9.19 uIU/ml, fT4 — 0.69 ng/ml, fT3 — 2.84 pg/ml. The patient was discharged from hospital in a good general condition. She remained under the care of an endocrinologist, who ended a one-month observation upon finding the patient in euthyreosis. The achievement of complete early viral response (cEVR) and low levels of initial HCV viremia, undetectable in the 24th week of treatment, justified the termination of the treatment with pegylated interferon alpha 2a and ribavirin. After six months of observation, HCV viremia was still undetectable (SVR) and the TSH and thyroid hormones levels, as well as complete blood count, were within normal limits.

Case no. 2

Female patient J.M., aged 52, treated for chronic hepatitis C with pegylated interferon alpha 2b (PegIFN alpha 2b) at a dose of 150 μg once a week and ribavirin at a dose of 1.2 g/day. The patient was infected with genotype 1 HCV. Before the treatment, the HCV viremia level was 2.52 × 10^6 IU/ml and the TSH level was 1.4 uIU/ml. Initially the treatment proceeded without complications. A decrease of viremia by 2 $\log_{10}$ (1.89 × 10^4 IU/ml) in the 12th week of therapy justified the continuation of the treatment. Due to anaemia (Hb 9.0 g/dl), the ribavirin dose was reduced

Table II. *The results of selected laboratory blood tests — case no. 2*
Tabela II. *Wyniki wybranych badań laboratoryjnych krwi — przypadek nr 2*

Laboratory results (normal values)	First day of hospitalisation	Third day of hospitalisation	Twelfth day of hospitalisation (last day)
Hb (12–16 g/dL)	9.6	8.0	12.2
Platelets (140–440 $\times$ $10^3/\mu$L)	196	183	261
Leukocyte (4–10 $\times$ $10^3/\mu$L)	0.8	1.0	5.4
Bands (3–5%)	0	0	8
Segments (57–65%)	2	0	25
Lymphocytes (20–40%)	97	99	56
Monocytes (4–8%)	1	1	11
Eosinophils (2–4%)	0	0	0
Basophils (0–1%)	0	0	0
ANC (1800–8000/μL)	16	0	1782
CRP (0–5 mg/dL)	347		28
PCT (< 0.5 ng/mL)	1.26		< 0.5

Hb — haemoglobin; ANC — absolute neutrophil count; CRP — C-reactive protein; PCT — procalcitonin

to 1.0 g/day. The TSH and thyroid hormones levels were within the normal range (TSH — 0.75 uIU/ml, fT4 — 0.96 ng/ml). In the 20th week of treatment, the patient reported a decrease in exercise tolerance, irritability and insomnia. No progression of anaemia was found. TSH was 0.20 uIU/ml and fT4 was 1.07 ng/ml. The TSH level was determined again after five weeks. At that time, hyperthyreosis was diagnosed (TSH < 0.005 uIU/ml, fT4 — 8.29 ng/ml) and the treatment with thiamazole at a dose of 20 mg/day was started. The interferon and ribavirin therapy was continued. After three weeks of taking thiamazole, the patient was admitted to hospital because of fever and chills of two days' duration, severe sore throat, difficulty in swallowing and enlarged cervical lymph nodes. Physical examination showed fever of 38.2°C, skin paleness, enlarged, soft and painful cervical lymph nodes. The patient presented with lockjaw, dysphagia and ulceration of the oral mucosa. Pharyngeal swabs and blood cultures were taken. All medications were discontinued. There were administered: hydrocortisone at a daily dose of 150 mg *i.v.*, fluconazole — 200 mg *i.v.*, meropenem 1.0 g *i.v.* three times a day and granulocyte colony-stimulating factor G-CSF (Neupogen) at a dose of 480 μg *s.c.* The general condition of the patient was stable, the sore throat and dysphagia were subsiding. On the third day of hospitalisation, the body temperature normalised. Pharyngeal swabs and blood cultures were negative. On the fifth day, the patient was transferred to the haematology department, where the treatment described above was continued. During her stay on that ward the patient again experienced fever, of 39.0°C. Purulent palatine tonsillitis was diagnosed. Enterococcus faecium was cultured from pharyngeal swabs and antibiotic was used according to the antibiogram result. The results of selected laboratory blood tests done during hospitalisation are presented in Table II. In the following three months of observation, the thyroid function returned to normal and the patient did not require further treatment. The treatment with PegIFN alpha 2b and ribavirin was not reinitiated due to its ineffectiveness (HCV RNA in the 24th week of treatment — 2.90 $\times$ 10^6 IU/ml).

Discussion

Recombinant or pegylated interferon alpha used in the treatment of chronic hepatitis C causes thyroid function disorders with an estimated incidence of between 5% and 15% [4]. Among factors predisposing to their development are female sex and the presence of antithyroid antibodies. The risk of developing thyroid dysfunctions in patients who had TPOAb before treatment is 46.1% compared to 5.4% in patients without these antibodies [5, 6]. It is recommended that TSH, fT4, TPOAb and TgAb levels be determined before treatment. During the treatment, the TSH test is repeated every 12 weeks in patients with a normal TSH level and without the antibodies, or every eight weeks if the antibodies are present [5, 7]. Hyperthyreosis occurs less frequently than hypothyreosis [8]. In the presented cases, hyperthyreosis developed in the 12th and 25th week of treatment with pegylated interferon alpha 2a and 2b respectively. In Poland the first-choice drug to treat hyperthyreosis is thiamazole. Propylthiouracil is reserved for patients with allergy to thiamazole and

for women in the first trimester of pregnancy [9, 10]. In both patients, thiamazole was used at first. However, in patient 1 due to the drug-intolerance it was replaced by propylthiouracil. Medications were administered at full dose, which resulted in euthyreosis.

A rare adverse drug reaction (affecting 0.2–0.5% of patients) is agranulocytosis [9]. In the discussed cases 1 and 2 it developed in the first three months of treatment with ATD and was of moderate and severe forms respectively. Anti-thyroid drugs were found to be the likely cause of agranulocytosis, although at the same time there were used two medications inducing bone marrow damage. Interferon alpha has a suppressive effect on bone marrow but agranulocytosis has never been reported while using the drug. In the registration study with pegylated interferon alpha 2b at a dose of 1.5 μg/kg/week and ribavirin, the necessity to reduce the dose due to neutropenia was 18%. Simultaneously, in less than 1% of patients the therapy was discontinued for that reason. In the registration study with pegylated interferon alpha 2a at a dose of 180 μg/week and ribavirin, the necessity to modify the dose due to neutropenia was 17% and only four patients (< 0.5%) terminated the therapy prematurely [12]. In Polish studies, neutropenia was the reason for discontinuation of the treatment in 0.6% of patients [13]. According to current guidelines, it is recommended to reduce the dose of pegylated interferon if the number of neutrophils falls below 750/mm^3, and to discontinue it altogether if the number is < 500/mm^3 [14]. These recommendations protect against the occurrence of agranulocytosis. Agranulocytosis prevention during the treatment with ATD consists in the frequent control of the leukogram. The number of neutrophils that suggest that the therapy should be discontinued is not clearly defined. Despite frequently performed haematology tests in the presented cases, the complication was not avoided. Granulocyte colony-stimulating factor was used in the treatment. It is said to be effective, though its effectiveness has not been unequivocally proved [9].

Hepatotoxic effects of anti-thyroid drugs were not observed in the female patients. Both imidazole and thiouracyl derivatives can cause drug-induced liver injury [15, 16]. Thiamazole induces mainly dose-dependent cholestasis, while propylthiouracyl induces dose-independent hepatitis. A communication issued by the FDA in June 2009 includes information on the heightened risk of severe liver injury after the use of propylthiouracil compared to thiamazole. In a case of treatment with the medication, it is recommended that patients be monitored for liver injury, particularly during the first six months of therapy [17].

In the cases discussed, close co-operation between the doctors treating patients with chronic HCV infection (in Poland mainly infectious disease specialists), endocrinologists and haematologists was necessary. Adverse drug reactions during interferon therapy, in particular thyroid dysfunction, require working closely with endocrinologists and making joint decisions as to continuation or discontinuation of treatment. The assistance of haematologists is indispensable in cases of severe agranulocytosis, when it is necessary to exclude its other causes and begin treatment with growth factors.

Conclusions

1. Anti-thyroid drugs used in the treatment of hyperthyreosis, being a complication after interferonotherapy, can cause agranulocytosis.
2. A synergistic effect of ATD and interferon on bone marrow cannot be excluded.
3. In a case of the occurrence of hyperthyreosis treated with ATD, the decision as to continuation or discontinuation of the antiviral therapy should be taken jointly by the doctor treating the patient with chronic HCV infection and an endocrinologist.

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