Case Report

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Neutropenia Due to Very Long Time Propylthiouracil Usage in Toxic Multinodular Goiter

Toksik Multinodüler Guatrda Çok Uzun Süreli Propiltiourasil Kullanımına Bağlı Nötropeni

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Abstract

Thyrotoxicosis affects hematopoiesis in several ways and thioamides may cause myelosuppression. We report a case of febrile neutropenia in a patient with hyperthyroidism who was using propylthiouracil for nearly 20 years for the treatment of toxic multinodular goitre. After surgery, the patient was euthyroid and neutropenia resolved. Postoperative pathology was evaluated as micropapillary thyroid carcinoma.
Keywords: Thyrotoxicosis, neutropenia, propylthiouracil

Öz

Tirotoksikoz çeşitli yollarla hemtopoezi etkiler ve tionamidlerle birlikte miyelosupresyona neden olabilir. Toksik multinodüer guatra bağlı 20 yıl gibi uzun bir süre propiltiourasil kullanan ve febril nötropeni nedeniyle hastaneye yatışı yapılan hipertirodili bir hasta sunduk. Total tiroidektomi olduktan sonra hasta ötiroid iken nötropenisi düzeldi. Postoperatif patoloji ise mikropapiller tiroid karsinomu olarak değerlendirildi.
Anahtar kelimeler: Tirotoksikoz, nötropeni, propiltiourasil

Introduction

It is well known that hyperthyroidism itself and thioamides both cause myelosuppression (1,2). While thionamides are responsible for most cases of the myelosuppression, some studies have suggested that toxic factors involving some essential metabolic pathways might be an underlying cause; thyrotoxicosis itself can also lead to myelosuppression because of immune mechanisms mediating the occurrence of granulocytopenia (3). We report a case of hyperthyroidism due to toxic multinodular goiter, nearly 20 years of propylthiouracil usage, severe neutropenia requiring hospitalization, and reversing after surgery.

Case Report

A 48-year-old female patient was admitted to the endocrinology outpatient clinic with the complaints of generalized fatigue, ulcers in the mouth, nausea, vomiting, shivering, and fever two years ago. She was taking propylthiouracil for the last 18 years at intervals because of neutropenia. Since she was living in a rural area, routine follow-up could not be done. On physical examination, her blood pressure was 100/60 mm/Hg, heart rate was 92 bpm, and body temperature was 37.7 °C. She had multiple small ulcers on oral mucosa and bilateral multiple nodules detected on thyroid examination. Laboratory parameters were: free thyroxine (fT_4): 2.14 ng/dl (0.61-1.12) free triiyodotironin (fT_3): 5.71 pg/ml (2.0-4.4), thyroid stimulating hormone (TSH): 0.02 µlu/ml (0.34-5.6); anti-thyroglobulin antibody and anti-microsomal antibodies: negative, leukocytes: 0.82x10^3 K/uL and neutrophil: 200 /mm^3. Peripheral blood smear was consistent with neutrophiles. The trachea was deviated to the right side and she had pneumonic infiltrate in the left lower lobe on chest x-ray (Figure 1). Thyroid ultrasound demonstrated multiple nodules bilaterally and the largest one in the left lobe measuring 38x22 mm was isoechoic. Thyroid scintigraphy showed multiple hyperactive and hypoactive nodules (Figure 2). The patient was referred to the hematology department. Bone marrow biopsy revealed normocellular bone marrow. Propylthiouracil was discontinued at admission. Imipenem+cilastatin sodium and teicoplanin therapy was initiated. During treatment, nodular opacity and ground glass appearance was seen in the laterobasilar segment of the left lobe on thoracic computed tomography (CT). Eight days after imipenem+cilastatin sodium and teicoplanin, amphotericin-B was added to the regimen due to high fever and negative cultures. Control leukocytes ranged

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between 2.5 and 3.5x10^{3}K/uL. One month after discharge, leukocyte count was 5.2x10^3 K/uL, neutrophil count was 2560/mm^3, fT_3 and fT_4 levels were elevated [fT_3: 13.1 pg/ml (2.5-3.9), fT_4: 2.90 ng/dl (0.61-1.12)], TSH level was 0.02 µlu/ml (0.34-5.6), thus, methimazole was started. After three days, she had fever (38.3 °C) and leukocyte count dropped to 0.60x10^3 K/uL. Methimazole was stopped and she was started imipenem+cilastatin sodium and granulocyte colony-stimulating factor (G-CSF). Neutrophil count rose to 2560/mm^3. She had never achieved euthyroidism thereafter and thyroidectomy was planned urgently. Potassium iodide solution 2x5 drops, prednisolone 60 mg/day and propranolol 3x20 mg were started. Before the operation, her laboratory results showed that she was euthyroid. Total thyroidectomy was performed. Histological examination revealed that the nodule examined in the left lobe was benign, but a papillary micro-carcinoma follicular variant was present in the right lobe (diameter=0.7 cm). She achieved euthyroidism in the follow-up with L-thyroxine and leukocyte count did not drop after thyroidectomy (Table 1).

Discussion

Thyrotoxicosis affects hematopoiesis in several ways, although clinically important abnormalities are rare. In the literature, there are a few case reports on hyperthyroidism associated with pancytopenia (4,5). Although the mechanism of pancytopenia in patients with hyperthyroidism is unclear, this may be related to the reduced life span of whole blood components partially due to the autoimmune mechanism or disturbances in the maturation and differentiation of the pluripotent stem cells. In this case, a bone marrow biopsy, which has showed normocellular marrow and no signs of atypia, was done. Granulopoiesis slows down and neutrophil survival is decreased in hyperthyroidism, additionally, in autoimmune thyroid disorders, antineutrophilic antibodies may develop which can all be responsible for cytopenia (3).

Propylthiouracil and methimazole are the most commonly used agents in the medical treatment of hyperthyroidism. Transaminase elevation and skin reactions can be seen during treatment.

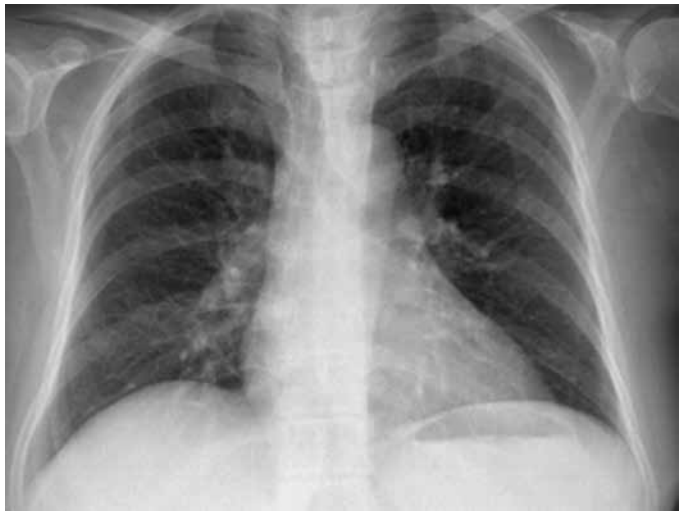

Figure 1. Chest x-ray showed trachea deviation to right and pneuomonic infiltration in left inferior lobe

Agranulocytosis is the most serious and feared complication of the medical therapy which might be seen in the first three months of treatment (6,7). 0.1-1% of patients treated with propylthiouracil have the risk of developing severe neutropenia (<500), while the majority may develop mild neutropenia (<1500) (8). Patients taking these treatments should be informed about symptoms of neutropenia, and regular complete blood count should be done (9). Leukocyte count is the simplest and accurate way of diagnosing agranulocystosis (10). G-CSF shortens the time of agranulocystosis. Minimum time to recovery from neutropenia after cessation of drug usage is five days, but mostly it takes one or two weeks (11,12,13). In our case, neutropenia recovered after G-CSF treatment, but neutrophil count did not rise up to 1500/mm^3. In this case, neutropenia worsened after thionomide usage but did not return to the normal for months, which can be explained by the disease nature that thyrotoxicosis itself can make agranulocystosis. After surgical removal of the thyroid gland, leukocyte and neutrophil counts were within the normal range. Neutrophil counts did not rise to the normal range after cessation of antithyroid drugs and remained in the lower limits (average 2.5-3.5x10^3 K/uL) during follow-up after thyroidectomy. The level of white blood cells was found to be normal only once (5.2 x10^3 K/uL) during the follow-up of 4 months that the patient was unmedicated. We thought that if we treat thyrotoxicosis, neutropenia might improve. Thus, we planned to switch from propylthiouracil to methimazole to keep the patient stable for surgery. Three therapeutic options are available for toxic nodules: surgery, 131-I therapy and ethanol injection. Antithyroid drugs can be used prior to definitive therapy if necessary, for example during pregnancy (14). This patient was followed by different clinics for several years, however, she has not attended regular follow-up visits in any of these clinics. Therefore, antithyroid therapy has continued without a long-term treatment plan. Radioiodine is a very effective therapy and over 25 years ago it had long term experiences. It can be choise in most patients particularly in older patients. Because it's easy and convinence slightly lower expense, avoiding from a scar, and avoiding from hospitalization (15).

Surgery is indicated for large nodules, especially when they have a large cystic component, in young patients. It consists of a total lobectomy and must be performed after restoration of an euthyroid by antithyroid drugs. After surgery, late hypothyroidism

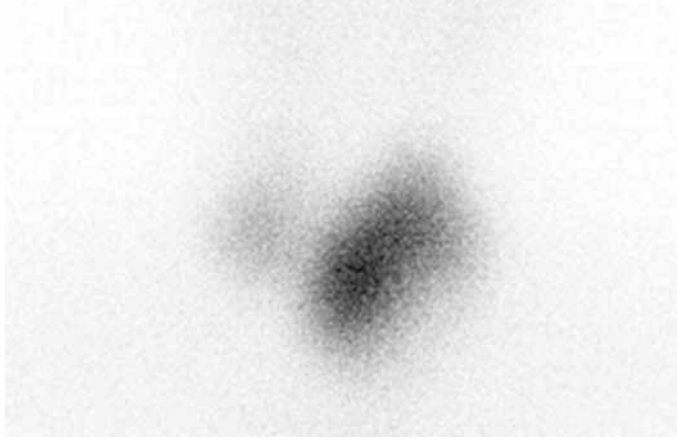

Figure 2. Thyroid scintigraphy showed multiple hyperactive and hypoactive nodules

Table 1. Changes in thyroid function tests and blood count

Date	TSH (Miu/ML) (0.35-5.4)	fT_4 (ng/dl) (0.61-1.12)	fT_3 (pg/ml) (2.5-3.9)	WBC (K/Ul) (4-10)	NEU (K/Ul) (1.5-7.3)	TGAb (IU/ml) (0-9)	TMAB (IU/ml) (0-40)
1. day	<0.004	3.59	10.8	3.2	1.1		
30. day	0.02	2.14	5.71	0.82	0.02		
34. day				1.77	0.49		
38. day				3.74	2.51		
46. day				2.98	1.76		
48. day	0.06	1.89	6.86	2.92	1.80		
54. day	0.02	1.49	10.26	2.18	1.06	4.0	0.7
60. day				2.69	1.35		
81. day	0.02	2.42	13.61	2.45	0.91		
105. day				5.27	2.56		
132. day	0.02	2.90	13.12	2.94	1.56		
142. day	0.01	1.37	3.43	3.19	2.05		
	Operation						
Postoperative 2. days				4.54	2.86		
Postoperative 4. month				4.53	2.94		
Postoperative 6. month				7.13	4.51		

TSH: Thyroid stimulating hormone, fT_3: Free triiodothyronine, fT_4: Free thyroxine, WBC: White blood cells, NEU: Neutrophils, TGAb: Thyroglobulin antibodies

may occur (30-40%) (15). We preferred thyroid surgery because of the recurrence risk after radioactive iodine treatment and her nodules were larger and multiple.

In conclusion, we believe that beside drug-induced agranulocytosis, thyrotoxicosis may induce neutropenia. In this manner; thyrotoxicosis itself may cause leukopenia and thionamides may worsen it. In these cases, permanent treatment should be performed as soon as possible.

Ethics

Informed Consent: Consent form was filled out by all participants, Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ahmet Kaya, Elif Turan, Mustafa Kulaksizoğlu, Bahar Kandemir, İbrahim Erayman, Design: Elif Turan, Data Collection or Processing: Elif Turan, Mustafa Kulaksizoğlu, Analysis or Interpretation: Elif Turan, Literature Search: Elif Turan, Writing: Elif Turan, Ahmet Kaya, Conflict of Interest: No conflict of interest was declared by the authors, Financial Disclosure: The authors declared that this study has received no financial support.

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