Pancytopenia in an untreated patient with toxic multinodular goiter

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ABSTRACT

Background: Thyroid abnormalities may be the cause of unexplained pancytopenia. Routine hematologic evaluation should be performed before administration of anti-thyroid drugs in cases of clinical hyperthyroidism, to clarify any occurrence of unexplained pancytopenia.

Case Presentation: An 82-year-old woman presented to the emergency department with general weakness, palpitations, excessive sweating, and weight loss. A complete work-up suggested the existence of hyperthyroidism due to toxic multinodular goiter with depletion of all three cell lines in peripheral blood count. Abdominal ultrasonogram showed no abnormal findings, including hepatosplenomegaly. Normocellular marrow was noted in bone marrow aspiration and biopsy.

Conclusion: A combined drug therapy with methimazole 30 mg/day, parenteral dexamethasone 8 mg/day, beta-blockers, and digoxin was administered to the patient. Free Triiodothyronine (FT3) and Free Thyroxine (FT4) levels decreased gradually and pancytopenia improved within 2 weeks of treatment.

Keywords: Goiter, pancytopenia, thyroid disease, case report.

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Background

Atypical manifestations of hyperthyroidism include hematological, cardiovascular, and dermatological manifestations. Single lineage abnormalities such as anemia (34%), leukopenia (5.8%), and thrombocytopenia (3.3%) are especially reported but pancytopenia is a rare presentation of hyperthyroidism. The possibility of hyperthyroidism should be considered in patients with unexplained pancytopenia [1,2].

The suspected etiologic mechanism includes ineffective hematopoiesis, reduction in blood cell lifespan, an autoimmune process, bone marrow suppression, and toxicity of thyroid hormone [3–5].

Clinical manifestations of cytopenias are variable and include recurrent, severe, or unusual infections that may be due to leukopenia/neutropenia; fatigue, dyspnea, chest pain, hemodynamic instability, claudication due to anemia, and bleeding or easy bruising due to thrombocytopenia or disseminated intravascular coagulation. Constitutional symptoms are usually present like fevers, night sweats, and/or weight loss [6].

Case Presentation

An 82-year-old Albanian female presented to the emergency room of our "Mother Theresa" Tirana University Hospital following a 6-weeks history of general weakness, palpitations, excessive sweating, weight loss, and increased stool frequency of normal consistency for up to 5 months. The past history was significant for toxic multinodular goiter diagnosed more than 10 years ago and she has been in treatment for a short period of time with thionamides. The patient did not have any history of a recent iodine load.

Clinically, the patient was a small-framed woman, pale, afebrile with a low-pitched voice. Her blood pressure was 100/60 mmHg, she had an irregular pulse of 120–130 beats per minute. Fine tremors were seen upon outstretching of hands and her palms were sweaty. She had an enlarged nodular goiter, non-tender, and no associated bruits. The electrocardiograph showed atrial fibrillation with rapid ventricular rate while she was on digoxin and beta-blockers for chronic atrial fibrillation. There was no thyroid acropathy, neither thyroid opthalmopathy nor pretibial myxedema. The patient had no other features to suggest any other associated autoimmune disease. Respiratory and abdominal examinations were unremarkable.

On hematological investigations, pancytopenia was observed. Thyroid function tests showed abnormally high concentration of free T4 = 83.39 (9–20) pmol/l and free T3 = 26.38 (4–8.3) pmol/l and Thyroid-stimulating hormone (TSH) = 0.004 (0.23–4.2) mUI/l. The patient was then admitted to the Endocrinology and Metabolic Diseases Service for further evaluation and treatment.

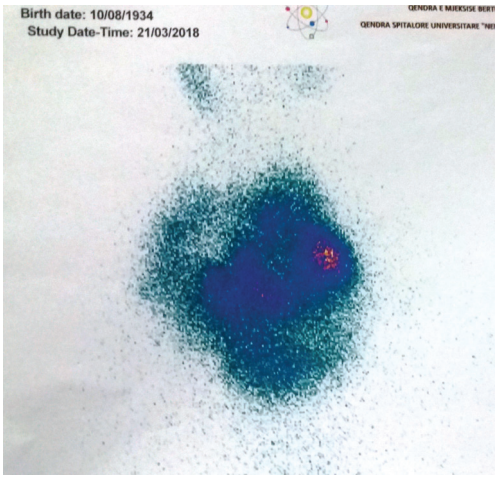

Figure 1. *Enlarged nodular thyroid gland with retrosternal extension and different areas of uptake.*

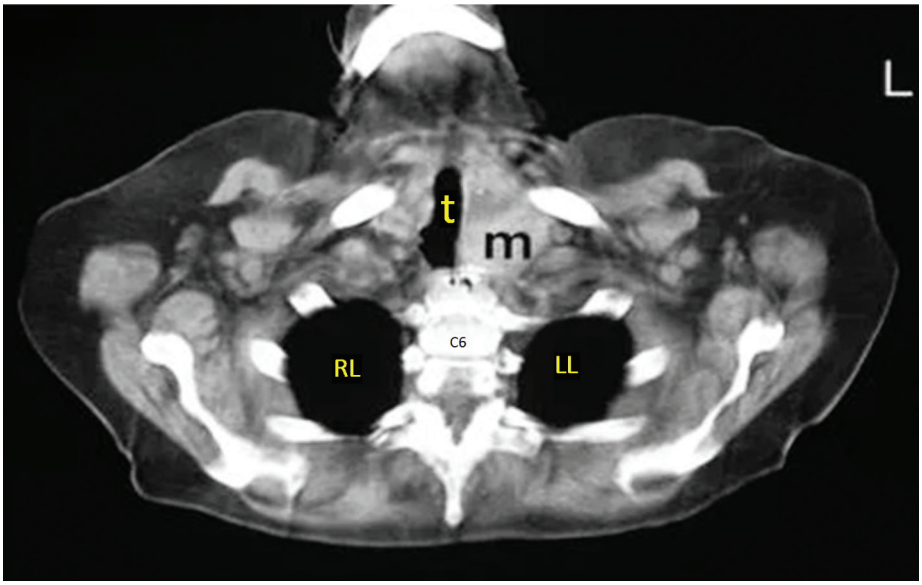

Figure 2. *Heterogeneous nodule with mass effect and retrosternal extension on the left thyroid lobe, displacing the trachea to the right (L—left side; t—trachea; m—mass effect of the left thyroid gland; C6—body of the sixth cervical vertebra; RL—right lung; LL—left lung).*

Upon admission, blood report was White Blood Cells (WBC) 3.2 K/µl, Hb 9.4 g/dl, and Platelet count (PLT) 17 K/µl. A normocytic, hypochromic anemia with thrombocytopenia was diagnosed, with no further abnormalities in the myelopoiesis or in the megakaryocytic morphology or functionality. Biochemistry profile and chest X-ray revealed the right deviation of the trachea. Thyroid ultrasound showed both lobes of thyroid enlarged, an isoechoic nodule on the left lobe with cystic degenerations and microcalcifications, measuring 3.2 cm and an isoechoic nodule measuring 1.6 cm on the right lobe and a few others appearing as cystic lesions, all less than 1 cm in size. Thyroid scan (Tc99mO4) noted an asymmetrical enlargement of the thyroid gland with hypo and hyperfixant areas of uptake (Figure 1). Abdominal ultrasonogram showed no abnormal findings, including hepatosplenomegaly. Echocardiogram showed good left ventricular function with ejection fraction of 62%, a left atrial enlargement, and moderate tricuspid regurgitation with a systolic pressure of pulmonary artery 40 mmHg. Thyroid computed tomography showed multiple nodules, with calcifications at the left lobe, retrosternal extension and right displacement of the trachea (Figure 2).

The patient was started on methimazole 30 mg/day and parenteral dexamethasone 8 mg/day while she was on beta blockers and digoxin for chronic atrial fibrillation. FT4 and TT3 levels decreased gradually (see Table 1) and pancytopenia improved after 2 weeks (see Table 2).

Discussion

Pancytopenia has been described in association with a wide variety of conditions (see Table 3). These conditions

Table 1. Plasma levels of thyroid hormones upon admission and after the second week of treatment.

THYROID HORMONE	UPON ADMISSION (PMOL/L)	AFTER THE SECOND WEEK OF TREATMENT (PMOL/L)	NORMAL VALUES (PMOL/L)
FT4	83.39	57.3	9–20
FT3	13.5	26.38	4–8.3

Table 2. Blood analysis values before and after the treatment.

PARAMETER	UPON ADMISSION	AFTER THE SECOND WEEK OF TREATMENT	NORMAL VALUES
Hemoglobin (gram %)	9.4	12.9	11–16.5 gr/dl
MCV	80	82	80–100 fl
MCH	27.9	28.3	25–32 pg
MCHC	34.1	34.0	28–36 g/dl
RDW-CV	13.4	13.9	<15.5%
WBC (*1,000 cells/mm^3)	3.5	7.5	4.0–10.0
Polymorphs	2.1	6.2	1.2–6.8
Lymphocytes	1.2	1.0	1.2–3.2
Monocytes	0.2	0.3	0.3–0.8
Platelets (*1,000/mm^3)	17	103	150–390

Table 3. Major causes of pancytopenia (adapted from [12,13]).

CAUSES OF PANCYTOPENIA	ACQUIRED	CONGENITAL
	* Bone marrow infiltration/replacement • *Malignant* o Acute leukemias o Chronic leukemias/myeloproliferative neoplasms (MPN) o Myelodysplastic syndromes (MDS) o Multiple myelomas o Metastatic cancer • *Non-malignant* o Myelofibrosis o Infectious (e.g., fungal, tuberculous) o Storage diseases * Bone marrow failure • Immune destruction/suppression o Aplastic anemia/paroxysmal nocturnal hemoglobinuria o Medications • Cytotoxic drugs • Idiosyncratic reactions to medications o Large granular lymphocyte leukemia o Autoimmune disorders [e.g., systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), sarcoidosis] Hemophagocytic lymphohistiocytosis (HLH) • Nutritional o Megaloblastic (vitamin B12, folate) o Excessive alcohol o Other (e.g., copper deficiency, zinc toxicity) o Malnutrition/anorexia nervosa with gelatinous degeneration • Marrow suppression o Viral infection [e.g., HIV, hepatitis, Epstein–Barr virus (EBV)] • Ineffective hematopoiesis (e.g., MDS, nutritional) * Destruction/sequestration/redistribution • Consumption o Disseminated intravascular coagulation (e.g., associated with sepsis, acute promyelocytic leukemia) • Splenomegaly o Portal hypertension/cirrhosis o Infections (e.g., EBV) o Autoimmune disorders (e.g., SLE, RA/Felty syndrome) o Malignancies (e.g., lymphomas, MPN) o Myelofibrosis with myeloid metaplasia o Storage diseases (e.g., Gaucher)	• Wiskott–Aldrich syndrome • Fanconi anemia • Dyskeratosis congenital/telomere biology disorders • Shwachman-Diamond syndrome • GATA2 deficiency • HLH

include bone marrow disorders (marrow failure syndromes, marrow space-occupying lesions, and ineffective marrow production), peripheral destruction of blood cells, infections, and drugs [7]. However, its association with hyperthyroidism has been observed in a number of case reports [1,2,8]. A particularity of the current case presented might be the prompt improvement of blood value parameters, i.e., within the second week of treatment, as well as the almost total therapeutic answer of all cellular lines (hemoglobin, WBC, and platelets whose number increased from 17 to 103 × 1,000/mm3 within this time frame).

Excess thyroid hormones can lead to ineffective hematopoiesis, and an autoimmune process has been imputed to induce antineutrophil or antiplatelet antibodies [9]. However, no specific tests were widely available to test specifically the immunological drive of thyrotoxic pancytopenia, and other available routine tests (such as thyroid binding inhibitory immunoglobulin, thyroid stimulatory immunoglobulin, thyroglobulin antibodies, and thyroid peroxidase antibodies) were mostly used and useful to evaluate the thyroid functionality itself [10].

Usually, marrow depression in thyrotoxicosis is treatment-related, due to methimazole or propylthiouracil, both of which may cause agranulocytosis. This patient actually developed pancytopenia prior to the administration of methimazole. Moreover, the delivery of standard anti-thyroid medication may be delayed, following concerns about drug-induced cytopenia [11].

Conclusion

Although the pathogenesis of hyperthyroidism-related pancytopenia is still not fully elucidated, it has been postulated that this condition is probably due to the reduction of the lifespan of blood cells that results from the immunological mechanism and increased destruction or sequestration of peripheral blood cells.

The causal effect of thyrotoxicosis in pancytopenia as in the current patient is best illustrated by the normalization of blood counts following reversal of thyrotoxic state [14]. Thyroid abnormalities may be the cause of unexplained pancytopenia; therefore, a routine hematologic evaluation should be performed before any administration of anti-thyroid drugs to differentiate a pancytopenia related to the thyrotoxic state itself, from the pharmacological bone marrow depression frequently induced by these drugs [11].

Acknowledgement

None.

List of Abbreviations

FT4	Free Thyroxine
FT3	Free Triiodothyronine
PLT	Platelet count
TSH	Thyroid-stimulating hormone
WBC	White Blood Cells

Consent for publication

Informed consent was taken from the patient.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

Patient (gender, age)	1	82 years old, female
Final Diagnosis	2	Toxic multinodular goiter; pancytopenia
Symptoms	3	General weakness, palpitations, excessive sweating, and weight loss
Medications	4	Methimazole; dexamethasone
Clinical Procedure	5	Bone marrow aspiration; thyroid computed tomography
Specialty	6	Endocrinology