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CASE REPORT

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Agranulocytosis: a rare complication of the thionamides

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Abstract

Agranulocytosis is a rare and life-threatening side effect of antithyroid drugs (ATD); it has been reported in < 0.2% of patients, usually within the first 3 months after starting ATD. We present a 62-year-old Libyan female patient who developed agranulocytosis 3 months after starting treatment with methimazole for hyperthyroidism. After 1 month of doubling her ATD dose, she developed a fever, sore throat, and generalized weakness for several days. Laboratory examinations revealed agranulocytosis (total leukocyte count was 1.14×10^3/μL, with granulocytes at 2.99% and lymphocytes at 93.21%). She was hospitalized, ATD was discontinued, and empirical antibiotic treatment was given. She was started on granulocyte colony-stimulating factor. Her cell counts improved, and she was discharged. The present case report aims to increase awareness of this potentially lethal adverse effect of ATD treatment. Patient education and close monitoring of high-risk patients are the key to reduce its morbidity and mortality.

Keywords Hyperthyroidism, Agranulocytosis, Neutropenia, Antithyroid drugs, Methimazole, Carbimazole, Propylthiouracil, Thionamides

Background

Hyperthyroidism is a condition resulting from the excessive production of thyroid hormones. Graves' disease and toxic multinodular goiter are the most common causes. The initial treatment of hyperthyroidism is with the antithyroid drug carbimazole or its active metabolite methimazole, while for propylthiouracil, Food and Drug Administration (FDA) have limited its use to the first trimester of pregnancy, and the thyroid storm, due to risk of hepatotoxicity [1, 2]. Minor side effects of antithyroid drugs like, skin rash, fever, and arthralgia occur in up to 5% of patients [1, 3]. These usually resolve spontaneously or after stopping and substituting with an alternative antithyroid drug [1, 3].

Rare but serious and life-threatening side effects include hepatitis, vasculitis, and agranulocytosis, which occur in 0.2–0.3% of adult patients taking ATDs. Agranulocytosis defined as absolute neutrophil count < 500/mm^3) has been reported in < 0.2%, generally within the first few weeks or months of treatment [3, 4]. The most common presenting symptoms are fever, malaise, and sore throat. More serious presentations are severe deep tissue infections, septicemia, and septic shock [4]. The pathogenesis is not completely understood. Immunologically mediated responses and direct toxicity were postulated [4, 5]. A specific polymorphism in human leukocyte antigen (HLA) genes has been associated with ATD-induced agranulocytosis. For example, HLA-B*27:05, HLA-B*38:02, and HLA-DRB1*08:03 alleles increase susceptibility to ATD-induced agranulocytosis [5].

A complete blood cell count with a differential leukocyte count is recommended before antithyroid drug therapy is initiated [1, 3]. A transient agranulocytopenia (granulocyte count, < 1500/mm^3) can be a manifestation of thyrotoxicosis itself, may occur during the first few weeks of antithyroid therapy, but can also be a herald of agranulocytosis. If serial measurements of the WBC count remain constant or return to normal, treatment

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can be continued. But if the WBC count shows a downward trend, the antithyroid drug should be stopped [1, 3].

Patients taking thionamides must be instructed to stop taking the medication immediately and contact their physician if they develop a sore throat, fever, or malaise [5]. In hospital admission, a broad-spectrum antibiotic is indicated. G-CSF may hasten the recovery [6].

Case presentation

A 66-year-old Libyan female 3 months back was diagnosed with hyperthyroidism, during a medical workup for dyspnea, which was progressive over 5 months until she became dyspneic on walking a few meters, her echocardiogram was normal, but thyroid function test disclosed hyperthyroidism: TSH, 0.001 μIU/mL (0.27–4.5 μIU/mL), FT4 36.9 pmol/L (reference range, 12–22), and FT3, 8.3 pg/mL (2.5–3.9). She was started on methimazole 30 mg/day and a beta-blocker for symptom management, prescribed by an endocrinologist in her city.

Two months later, her methimazole dose was increased to 60 mg/day, because of a persistent symptom. One month later, she presented to her local doctor with fatigability, fever, headache, and sore throat. Azithromycin was prescribed with no improvement. Her CBC showed neutropenia. She was advised to stop ATD and referred to the endocrine department, at the university hospital.

She is type-2 diabetes for 12 years on premixed insulin, Janumet (sitagliptin 50 mg/metformin 850 mg) BD, simvastatin 20 mg OD, and aspirin 75 mg OD. Occasionally, she took paracetamol tablets for her osteoarthritis. Upon admission, the initial assessment of vital signs revealed a temperature of 38.5 °C, heart rate of 102 beats/min, and blood pressure of 150/80 mmHg. Respiratory rate is 16/min.

On physical examination, the patient was conscious, oriented, not jaundiced, not pale, no ophthalmopathy, and mild thyroid gland enlargement. Her JVP was not raised and no peripheral edema or lymphadenopathy.

Pericardium, chest, and abdominal examination revealed no abnormalities. Peripheral blood count showed microcytic hypochromic anemia. Her hemoglobin was 9.13 g/dL (reference range, 12–18 g/dL), and platelet count was 214×103/μL (reference range, 150–350×10^3/μL). Total leukocyte count was 1.14×10^3/μL (reference range, 4–9×10^3/μL), and the absolute neutrophil count was 0.03×10^3/μL (reference range, 1.10–7.0×10^3/μL). Differential showed the following: 2.99% neutrophils, 93.21% lymphocytes, 0.00% monocytes, 3.35% eosinophils, and 0.45% basophils. The patient's baseline complete blood count, prior to methimazole initiation, was not available.

The result of thyroid function tests was as follows: thyroid-stimulating hormone (TSH) 23.4 μIU/mL (reference range, 0.27–4.5) and free T4 3.7 pmol/mL (reference range, 12–22).

Biochemical analysis is as follows: Cr 0.56 (0.7–1.2 mg/dl), urea 20.2 (6–45 mg/dl), Na = 135.8 mmol/L, K = 4.55 mmol/L, Cl = 102.3 mmol/L, total bilirubin 0.850 (0.1–1.2 mg/dL), direct bilirubin 0.362 (0–0.3 mg/dL), AST 15 (0–40 U /L), and ALT 12 (0–41 U /L), random blood glucose = 143 mg/dL, and HBA1C = 8.5%. C-reactive protein level was high at 120 mg/L (reference range, 0–5 mg/L). Her chest x-ray was normal; abdominal ultrasound showed a calcified splenic hydatid cyst. Echocardiogram: *EF* = 69%, good LV function.

Thyroid ultrasound examination showed a hypoechoic round nodule 11 mm × 12 mm × 14 mm in the left thyroid lobe and a cystic lesion in the right thyroid lobe measuring 3 mm × 3 mm × 4 mm. Thyroid antibodies were not available. The patient was diagnosed with methimazole-induced agranulocytosis. Methimazole was discontinued immediately, and the patient was admitted to the hospital, in an isolation room, and started empirically on an intravenous broad-spectrum antibiotic (4th-generation parenteral cephalosporin) cefepime 2-g q8h. On the 4th admission day, she was started subcutaneous Neupogen (G-CSF) 300 μg once daily for 3 days. On day 11, her total leukocyte count was 4.91 10^3/μL, and differential count was as follows: neutrophils 1.55 (31.56%), lymphocytes 2.54 (51.7%), monocytes 0.74 (15.16%), eosinophils 0.0 (0.0%), and basophils 0.08 (1.58%). On day 12, she was discharged on her diabetes medication and beta-blockers. Four days post-discharge, her CRP was 4.66, hemoglobin was 10.5 g/dL, and total leukocyte count was 7.62×10^3/μL, with neutrophils 4.2 (55.2%) and lymphocytes 2.6 (34.4%). TSH 1.56 was μIU/mL (0.27–4.5), FT4 0.882 (0.932–1.71), and FT3 0.300 ng/dl (0.202–0.443). Ten days post-discharge, she received 10 mci I131. The radioiodine uptake scan result was not provided. One month later, her TSH was 1.9 μIU/mL (reference range, 0.27–4.5), and total T4 was 66.6 ng/mL (reference range, 52.0–127).

Discussion

Carbimazole (CZ) is a precursor of methimazole (MZ) and was the only drug prescribed for hyperthyroidism in Libya. Recently, methimazole becomes available in private pharmacies [3]. The usual initial CZ dose is 45 mg given in three divided doses and then titrated down to a maintenance dose of 5 to 10 mg daily [1, 3, 7]. The European Thyroid Association guidelines recommend the initial dose depending on the severity of hyperthyroidism [7]. Antithyroid drugs associated with serious side effects include agranulocytosis, vasculitis, and hepatotoxicity. Agranulocytosis is defined as a granulocyte count < 500 cells/μL [4]. The estimated

incidence of agranulocytosis is < 0.2%, and 85% of cases were observed within 3 months of starting ATD [6–8]. Agranulocytosis risk is dose dependent, and high-dose regimens carry a 10-fold higher risk compared with low dose.

In the present case, agranulocytosis developed 3 months after the initiation of methimazole, and 1 month after, the thiamazole dose doubled to 60 mg/day. The European Thyroid Association guidelines recommend an initial dose of 10 to 30 mg of methimazole once daily depending on the severity of hyperthyroidism [7]. Besides the high risk of agranulocytosis associated with higher ATD doses, high doses can cause iatrogenic hypothyroidism in patients with mild disease.

The American Thyroid Association guidelines suggest a rough guide to initial methimazole daily dosing of 5–10 mg if free T4 is 1–1.5 times the upper limit of normal, 10–20 mg for free T4 1.5–2 times the upper limit of normal, and 30–40 mg for free T4 2–3 times the upper limit of normal [1].

In our case, with a free T4 of 36.9 pmol/L, a dose of 30 mg a day would be sufficient. The mean age of reported cases is 43.4 years, and the risk is 6.4 times greater in patients older than 40 years [8]. Our patient presented with typical complaints of ATD-induced agranulocytosis, sore throat, and fever; 100% of cases presented with fever and 76.9% with a sore throat [9].

Although agranulocytosis is uncommon, it is a life-threatening complication with mortality rates up to 18% if not diagnosed and managed early [10].Old age, a neutrophil count $\leq 0.1 \times 10^9$/L, 100/μL, and presentation with septicemia or septic shock carry a poor prognosis.

Patients with a neutrophil count less than 100/μL have a greater risk of serious infectious and fatal complications than do patients with a higher neutrophil count. In our case, her initial granulocyte count was 30/μL which in addition to her age put her in the high-risk category for serious deep tissue infections and death [9, 11].

It is important to monitor patients with high-risk factors for poor outcomes more closely especially in the first 3 months of initiating therapy [1, 7]. Once diagnosed, antithyroid drugs should be stopped, and patients should be hospitalized. The leukocyte count usually starts to normalize within 1–2 weeks of drug discontinuation, if there are enough myeloid precursor cells present in the bone marrow; however, with granulocyte precursor aplasia, a prolonged recovery is expected [4].

Currently, many experts recommend the use of G-CSF in drug-induced agranulocytosis, especially for patients with poor prognosis (including the presence of renal, cardiac, or respiratory failure, severe infection, age > 65 years, or neutrophils < 100 cells/μL) [11, 12].

Treatment of ATD-induced agranulocytosis by G-CSF has been reported to decrease the mortality rate from 21.5 to 5% [11, 12].

The mean recovery time in patients with G-CSF therapy is 6.8 days. After recovery from agranulocytosis, prescribing alternative ATD should be avoided due to common cross-reactions among thionamides [1, 7].

In patients who have developed ATD-induced agranulocytosis, definitive therapy with radioactive iodine or surgery is recommended [1, 7].

Patients need to be given clear instructions to stop the medication and consult their doctors if developed signs and symptoms of agranulocytosis like fever or sore throat [1, 7].

The methimazole package insert in Japan includes a strong warning to check blood counts every 2 weeks for the first 2 months of therapy [9]. Using this, Tajiri reported that they successfully diagnosed 78% of agranulocytopenia cases before the onset of symptoms by periodically checking blood counts [13].

Conclusions

ATD-induced agranulocytosis is a rare but serious adverse effect of thionamide drugs. Older patients and those on high doses are at greater risk. Patients should be warned about this side effect both verbally and in writing. Reinforcing education at each visit is recommended, especially in the first 3 months of treatment and for those at high risk of this life-threatening complication.

Abbreviations

ATD	Antithyroid drug
PTU	Propylthiouracil
WBC	White blood cell
CBC	Complete blood count
G-CSF	Granulocyte colony-stimulating factor

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Authors' contributions

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Availability of data and materials

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Verbal informed consent was obtained from the patient to allow us to publish a report of his case for educational purposes. The case report has been completely anonymized.

Competing interests
The author declares no competing interests.

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