METHIMAZOLE-INDUCED AGRANULOCYTOSIS AND SEPSIS: WAS THYROID STORM PRESENT OR JUST BEING MIMICKED?

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Abstract

Introduction. Agranulocytosis induced by thioamides is rare, occurring only in 0.2-0.5% of cases.

Case presentation. We present the case of a 45-year-old woman previously diagnosed with Graves' disease that discontinued the use of methimazole on her own. She attended the Emergency Department presenting fever (40.5°C), agitation and diaphoresis. A thyroid storm diagnosis was initially thought, but after laboratory results showing neutrophil count near $0.06 \times 10^9/L$, sepsis due to neutropenia seemed the most logical hypothesis. Cephepime was promptly initiated. For thyrotoxicosis management, cholestyramine and atenolol were prescribed. In her second day of hospitalization, subcutaneous granulocyte colony-stimulating factor was started for an earlier medullar response. The patient was discharged after 7 days with atenolol 50mg/day and instructed to have a definite treatment for Graves disease as soon as possible.

Conclusion. Such case purpose is to remember clinicians that sepsis diagnosis can be challenged, especially when a thyroid storm is a possible diagnosis as well. In this particular case, both conditions should be treated, but life-threatening sepsis should have the focus for a quick therapeutic approach.

Key words: Agranulocytosis, Methimazole, Thyroid Crisis, Sepsis, Graves' disease.

INTRODUCTION

Antithyroid drug therapy is an alternative for the treatment of hyperthyroidism, achieving remission in about 50% of patients with Graves' disease. Options include propylthiouracil, carbimazole and its active metabolite methimazole (all members of the thioamide class). In clinical practice, propylthiouracil is being replaced by carbimazole and methimazole since their biological half-lives are longer (1-2h vs. 3-5h for methimazole and carbimazole, with no differences between them) (1).

Agranulocytosis is a rare complication of

thioamides, occurring in about 0.2-0.5% of cases. Sepsis in the setting of neutropenia is rapidly fatal if untreated and represents a medical emergency (2).

Once patients who experienced an episode of thionamide-induced agranulocytosis can no longer use this drug class, definitive treatments such as total thyroidectomy or radioactive iodine therapy should be considered as first-line therapy (3).

It is important to note that a thyroid storm is often mistaken for sepsis since they both have the same cardinal features: tachycardia, diaphoresis, agitation, fever and altered level of consciousness. These two diagnoses can often be mistaken especially in patients with uncontrolled hyperthyroidism (2).

We present a case report of a patient with methimazole-induced agranulocytosis accompanied with sepsis mimicking a thyroid storm weeks after thioamide discontinuation.

CASE REPORT

A 45-year-old woman attended the Emergency Department experiencing fever (40.5°C), agitation and diaphoresis. She had a previous diagnosis of Graves' thyrotoxicosis in 2015 with irregular use of methimazole 40mg/day (last dose 3 weeks ago) followed up in another institution. Upon physical exam, a diffuse grade 2 goiter was noted, tachycardia at 143 bpm, hypotensive 90x50 mmHg, body mass index 24.3 kg/m². No other abnormalities.

Clinical features made thyroid storm (due to history of irregular methimazole use) and sepsis as differentials. Laboratory tests (Table 1) show WBC count of $0.43 \times 10^9/L$ with only 15% neutrophils (equivalent to $0.06 \times 10^9/L$). Considering this result, sepsis seemed the most probable diagnosis. She had a Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) score of 2 with hypotension and altered mental status, but lactate was below 2 mmol/L not meeting the

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criterion for septic shock yet. Cephepime 1g twice a day was promptly initiated; shock responded well to volume intake and no vasopressor was needed. Due to clinical improvement, we did not initiate empirically anti-fungal agents.

No source of infection was identified (chest x-ray and urinalysis were normal). No lumbar puncture or brain image study were performed due to the absence of major neurological features. Blood, urine and induced sputum cultures were then collected.

In addition, an evaluation by the oncology team was requested. They discarded some neutropenia differentials such as autoimmune diseases, viral etiologies, vitamin deficiency (Table 1), and hypothesized that it could be methimazole-induced agranulocytosis. They prescribed on day 2 filgrastim (subcutaneous granulocyte colony-stimulating factor – GCSF) 300 µg subcutaneously for earlier medullar recovery. Figure 1 shows neutrophil count evolution during hospitalization days.

For thyrotoxicosis management, the endocrinology team instructed the initiation of cholestyramine 4g twice a day (not beta-blocker given the initially hypotensive condition). The patient was put in contact isolation and no intensive care was needed. On day 2 of hospitalization, after blood pressure normalization, atenolol 50mg/day was initiated for thyrotoxicosis management. Irregular fever peaks continued until day 3. Culture results were negative.

She was discharged after 7 days of hospitalization with strict precautions against taking

methimazole or propylthiouracil, prescribed with atenolol 50 mg/day and instructed to seek as soon as possible her endocrinologist for a definitive treatment (surgery or radioactive iodine).

DISCUSSION

Neutropenic fever is characterized by a temperature above 38°C and less than 1500 neutrophils per microliter (equivalent to $1.5 \times 10^9/L$), being a severe neutropenia characterized by less than 500 cells per microliter ($0.5 \times 10^9/L$). There are numerous potential causes for this syndrome: medication use (chemotherapy, thioamides, clozapine, trimethoprim-sulfamethoxazole), infections (HIV, hepatitis B, influenza, tuberculosis), autoimmune diseases and nutrition (B12 or folate deficiency) (4).

The most common presentation is an unexplained fever with no clinically identified infection source and no identified pathogen in microbiology studies. Actually, only 20-30% of febrile neutropenia have clinically documented infection with a positive culture. Broad spectrum antibiotics should be empirically started within 1 hour, being cephepime, meropenem or piperacillin-tazobactam as the first-line therapy. Fungal infection should be considered if the fever persists after 4 to 7 days of antibiotics or if patients remain hemodynamically unstable. Similarly, empiric treatment with antiviral therapy is not indicated unless there is evidence of acute viral infection (4).

Agranulocytosis caused by thioamides is a rare adverse outcome which may occur at any time during therapy and at any dose. It usually occurs within the first 90 days of medication use and is dose-related (the higher the dose, the more likely the probability of

Table 1. Laboratory test exams at day 1 of hospitalization

Admission laboratory test	Result
Haemoglobin	11.2 g/dL
White blood cells	$0.43 \times 10^9/L$
Neutrophils	15%
Lymphocytes	83%
Platelet	$206 \times 10^9/L$
Glucose	102 mg/dL
Antinuclear antibodies	negative
Rheumatoid factor	negative
HIV, VDRL, hepatitis B and C	negative
Epstein-Barr and cytomegalovirus	IgG positive
Vitamin B ₁₂	267 pg/mL
Urea	20 mg/dL
Creatinine	0.54 mg/dL
Sodium	139 mmol/L
Potassium	3.9 mmol/L
Lactate	1.3 mmol/L
C-reactive protein	20 mg/dL
TSH	<0.01 µU/mL
Free T4	4.13 ng/dL
Total T3	178 ng/dL

Figure 1. Neutrophil count by hospital day / Day 1- Cephepime and cholestyramine started; Day 2- Filgrastim and atenolol started; Day 6- Filgrastim discontinued; Day 7- Discharge with atenolol.

developing it). Exceptions exist, as the case reported by Mutharasan *et al.* with agranulocytosis occurring only after 10 years of exposure (5). It is important to emphasize, however, that a complete blood count during methimazole therapy is not routinely recommended because agranulocytosis usually develops quickly within days (2).

There are only two cases in the medical literature reporting that agranulocytosis can be caused by thioamide discontinuation after weeks or months. Uçler *et al.* reported agranulocytosis in a patient who stopped methimazole use for 3 weeks and 10 days due to irregular menstrual cycle (6). Bai *et al.* also reported a patient who developed agranulocytosis after 4 months without receiving methimazole (7). In our patient that seemed the case, since she referred discontinuation of thioamide weeks before (explained by the thyroid altered function laboratory exams), and still did present agranulocytosis.

This idiosyncratic drug reaction is not entirely known. A possible mechanism is that the myelosuppression effect on granulocyte production occurs due to anti-granulocyte autoantibodies and/or direct toxicity at the hematopoietic stem cell level (1, 3).

Treatment usually includes suspending the drug and avoiding it in the future due to its cross-reactivity (2). Besides that, specific treatment for neutropenia includes the use of GCSF agents. Although its routine use is not recommended, several studies have shown that GCSF decreases episodes of neutropenic fever, documented infection, and hospitalization rates and are effective in shortening the recovery time of methimazole-induced agranulocytosis (2, 4, 7).

Given our patient's irregular treatment, thyroid storm was a differential to explain the fever, tachycardia, diaphoresis and other thyrotoxicosis symptoms. Actually, the misdiagnosing of sepsis and thyroid storm is complicated. Our patient had a Burch-Wartofsky Point Scale for thyrotoxicosis of 65 (temperature $\geq 40^{\circ}\text{C}$, agitation, heart rate ≥ 140 bpm), indicating a "highly" suggestive thyroid storm. The presence of hypotension and severe neutropenia is much more suggestive of a sepsis diagnosis.

Rayner *et al.* had the same difficulty to diagnose a sepsis mimicking thyroid storm. Free T4 in that patient was 3 ng/dL, not too increased, but there are no specific values to differentiate thyroid storm from uncomplicated hyperthyroidism (2). We, therefore, suggest that a patient in doubt between sepsis and thyroid storm should be treated for both conditions,

especially because thyroid storm is diagnosed based only on clinical features.

Other pharmacological therapies should be assessed for hyperthyroidism control when thioamides cannot be used. Propranolol or another beta-blocker is classically used to attenuate adrenergic symptoms, such as tremors. They act by inhibiting the peripheral conversion of T4-T3. Another option is the use of cholestyramine, which eliminates thyroid hormones that are free in the intestine, lowering their reabsorption. Lugol iodine (potassium iodide) is usually prescribed before thyroidectomy, because of its capacity to reduce thyroid vascularity and the risk of bleeding during surgery. Lithium has several mechanisms of action in the treatment of thyrotoxicosis, the main being the inhibition of iodotyrosine residues preventing T4 and T3 synthesis. At last, corticosteroids also reduce the conversion of T4 to T3, being used as well for Graves' ophthalmopathy (3, 8, 9).

Definitive treatment with total thyroidectomy and radioactive iodine are options as well. In general, the patient should be clinically stable and euthyroid for this approach. Nevertheless, a recent case report did indicate total thyroidectomy in a septic patient with thioamide-induced agranulocytosis with T3 and free T4 still increased. Even with the lack of clinic stability, the patient was refractory to all therapeutic options (lithium plus cholestyramine plus Lugol plus propranolol) and the benefit of thyroidectomy was greater than the risk of surgical complications (3).

In the present case, we preferred to treat and resolve the sepsis' episode before indicating the definitive treatment. We opted for beta-blockers plus cholestyramine, and the patient responded well. Lithium and corticosteroids could be used as options if thyrotoxicosis symptoms were not controlled. Lugol, on the other hand, should be avoided as first medication, because it can exacerbate hyperthyroidism symptoms in the first days (just like radioactive iodine, for example).

It is important to remember that corticosteroids do not have a remarkable role in sepsis and should not be initiated for everyone with that diagnosis. In fact, the recent article of ADRENAL trial that randomized 3,800 patients with septic shock aimed to assess the true effectiveness of hydrocortisone in early treatment of this highly lethal disease. It demonstrated a shorter duration of the initial episode of mechanical ventilation and faster resolution of shock in the group receiving hydrocortisone. However, once again, it failed to prove mortality reduction in the group treated

with hydrocortisone (10). Thus, the indication for hydrocortisone use only in refractory noradrenaline septic shock remains.

This case, to the authors' best knowledge, is the first to report two rare entities at the same time: 1) methimazole-induced agranulocytosis accompanied with sepsis mimicking thyroid storm and; 2) agranulocytosis after methimazole discontinuation.

Such case purpose is to remember clinicians that sepsis diagnosis can be challenged. Since thyroid storm is a clinical scoring based diagnosis we suggest its treatment independent of free T4 or T3 values, but life-threatening sepsis should have the focus for a quick therapeutic approach. As for the agranulocytosis, broad-spectrum antibiotics should be initiated within 1 hour if fever is present and GCSF is an important support therapy for earlier medullar recovery.

Conflict of interest

The authors declare that they have no conflict of interest.

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