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Bullous Dermohypodermitis Revealing Agranulocytosis Induced By Synthetic Antithyroid Drugs: A Diagnostic Pitfall

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Abstract: Original Research

Introduction: Agranulocytosis induced by synthetic antithyroid drugs is a rare but serious complication of hyperthyroidism treatment, usually presenting with symptoms of a common infection. Severe cutaneous manifestations are exceptional. ***Case report:*** We report the case of a 58-year-old female patient treated with high-dose methimazole for hyperthyroidism, admitted with extensive bullous dermohypodermitis of the upper limb and ipsilateral chest wall, associated with a deterioration in her general condition. Laboratory investigations revealed severe agranulocytosis complicated by a major inflammatory syndrome. Imaging ruled out necrotising fasciitis. Immediate discontinuation of synthetic antithyroid drugs, initiation of empirical antibiotic therapy and multidisciplinary management led to a favourable clinical and laboratory outcome. ***Discussion:*** This observation highlights an unusual and misleading presentation of agranulocytosis induced by synthetic antithyroid drugs, which can constitute a genuine diagnostic pitfall. The prescription of high initial doses, the absence of prior laboratory investigations, and the concomitant use of corticosteroids likely contributed to the severity of the clinical picture. This case underscores the importance of heightened vigilance in the face of any severe infection in a patient being treated with antithyroid drugs. ***Conclusion:*** Bullous dermohypodermitis may, in exceptional cases, reveal agranulocytosis induced by antithyroid drugs. Prescribing in accordance with guidelines, appropriate monitoring and clear patient information are essential to prevent this serious complication.

Keywords: Agranulocytosis, Synthetic Antithyroid Drugs, Methimazole, Bullous Dermatitis, Hyperthyroidism.

INTRODUCTION

Synthetic antithyroid drugs, primarily methimazole, carbimazole and propylthiouracil, form the cornerstone of medical treatment for hyperthyroidism, with proven efficacy in numerous clinical forms of Graves' disease and other causes of thyrotoxicosis [1, 2]. Despite their widespread use, these drugs carry a risk of adverse effects, amongst which agranulocytosis stands out as a rare but potentially fatal complication, with an estimated incidence of between 0.1 and 0.5% of treated patients [3, 4]. Female gender, age over 40, and the first three months of treatment with antithyroid drugs are identified in the literature as risk factors for agranulocytosis.

Agranulocytosis is defined as a neutrophil count (< 500/mm³) and exposes the patient to a high risk of infection, which can lead to septic shock if not treated promptly [3, 5]. Classic clinical presentations are dominated by fever, upper respiratory tract infections or severe tonsillitis [4, 6]. Cutaneous manifestations, particularly extensive bullous dermohypodermitis as the presenting feature, are exceptionally rare.

We present here an unusual clinical case of bullous dermohypodermitis revealing agranulocytosis induced by synthetic antithyroid drugs, highlighting the importance of adhering to dosage recommendations and of clinical and laboratory monitoring.

Clinical Case

Patient B. F., aged 58, with no known history of allergies or infections, who has been under treatment for hyperthyroidism for one and a half months, started on 60 mg/day of methimazole without initial blood tests or close monitoring, Prednisolone 40 mg; diagnosed with type 2 diabetes one month ago with an HbA1c of 7.4%, placed on lifestyle and dietary management; no other known conditions, notably no hypertension, no nephropathy, no heart disease, no active tuberculosis or history of tuberculosis, and no known autoimmune disease.

She was admitted in the emergency departement with erythematous-bullous lesions on her arm and the ipsilateral chest wall, which had been developing for one week, accompanied by a feeling of fever and a deterioration in her general condition.

On examination, the patient was conscious, haemodynamically and respiratorily stable, with no signs of shock. The examination revealed diffuse tenderness and a warm, painful inflammatory rash with ruptured blisters on the arm and the ipsilateral chest wall.

Further investigations revealed a leukopenia of 1,750/mm³ with a neutrophil count of 30/mm³, C-reactive protein at 223 mg/L, hyponatraemia at 120 mmol/L, blood glucose of 3 g/L, thyroid function tests showing low free T4 (T4 = 5.14 pmol/L) and severely reduced free T3 (T3 < 1.65), and normal liver and kidney function tests.

Soft tissue ultrasound revealed significant subcutaneous and supra-aponeurotic soft tissue infiltration, more pronounced at the posterolateral wall of the upper third of the left arm, with no clearly detectable collection. Venous Doppler ultrasound of the left upper limb showed no thrombosis.

Management consisted of the immediate discontinuation of synthetic antithyroid drugs. The patient was placed on broad-spectrum empirical antibiotic therapy (amoxicillin-clavulanic acid), local care and haematological monitoring via daily complete blood counts (CBCs). She was also placed on insulin.

Her condition improved rapidly, with regression of the skin lesions and normalisation of the neutrophil count (2,660/mm³).

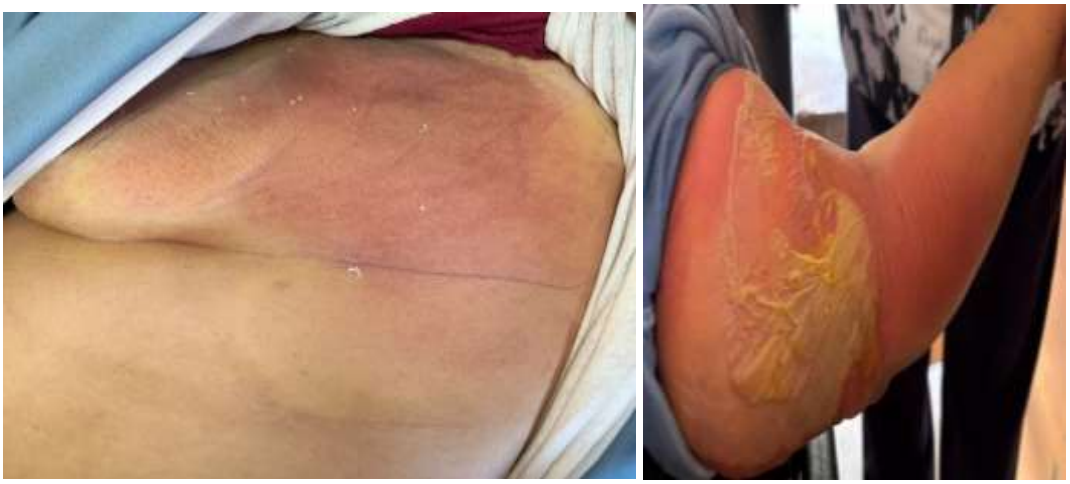

Figure 1: Before, in the emergency departement

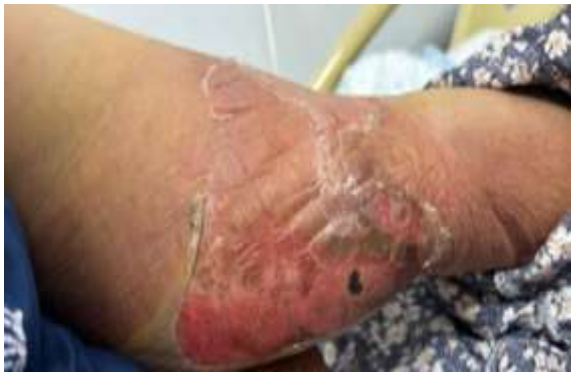

Figure 2: 5 days after discontinuation of ATS (in hospital)

DISCUSSION

Agranulocytosis induced by synthetic antithyroid drugs is a rare but serious complication, potentially fatal complication, with an incidence of 0.1–0.5%, generally occurring within the first few months of treatment [3, 4]. It is characterised by a sudden drop in neutrophil counts, leading to severe immunosuppression.

The pathophysiological mechanism is not fully understood; however, two main hypotheses are traditionally and frequently put forward: direct bone marrow toxicity and an idiosyncratic immuno-allergic reaction [2, 7]. Although agranulocytosis can occur regardless of dose, several studies have shown an association between high initial doses of methimazole (≥ 30–40 mg/day) and an increased risk [3, 8].

Typically, agranulocytosis associated with synthetic antithyroid drugs presents with common infectious symptoms such as fever, sore throat or upper respiratory tract infections [4, 6]. Deep skin infections are less common and have been described mainly in clinical series of severe neutropenia [9]. A case of soft tissue infection complicating drug-induced agranulocytosis was reported by Karaşahin and İba-Yılmaz, highlighting the possibility of severe cutaneous presentations [10]. However, extensive bullous dermohypodermitis as an initial presentation remains exceptionally rare.

The distinctive feature of our case lies in the bullous, extensive and misleading nature of the skin lesions that revealed the agranulocytosis. Such a clinical picture may suggest several serious differential diagnoses, such as necrotising fasciitis, severe drug eruption or an autoimmune bullous dermatosis with secondary infection [11]. The absence of fluid collection on imaging, the good response to empirical antibiotic therapy and the rapid recovery of neutrophil counts following discontinuation of synthetic antithyroid drugs allow these other diagnoses to be ruled out.

Concomitant corticosteroid therapy also represents an aggravating and confounding factor, potentially masking inflammatory signs and delaying the onset of fever or classic symptoms [7, 9].

To our knowledge, no major series has reported extensive bullous dermohypodermitis as the clinical manifestation of agranulocytosis induced by synthetic antithyroid drugs, which makes this case unique and highlights a significant diagnostic pitfall for the endocrinologist and clinician [3–6, 9].

Furthermore, the current guidelines from the American Thyroid Association recommend adjusting the doses of synthetic antithyroid drugs according to the clinical and biological severity of hyperthyroidism, whilst monitoring for expected adverse effects [11, 12]. A moderate initial dose of methimazole (10–30 mg/day) is often sufficient, with subsequent adjustments based on changes in TSH and thyroid hormone levels [1, 12]. Regular laboratory monitoring, particularly monitoring of the complete blood count (CBC) in the event of symptoms of infection, remains essential.

Immediate discontinuation of synthetic antithyroid drugs upon the onset of agranulocytosis is imperative. Administration of granulocyte colony-stimulating factors (G-CSF) may be considered in cases of persistent severe neutropenia [5, 13]. Reintroduction of an ATS is contraindicated [14]. Therapeutic alternatives include plasmapheresis, Lugol's solution to prepare for radical treatment with radioactive iodine, or surgery once the infection has been stabilised [12, 15].

Finally, patient education is essential: patients must be made clearly aware that they

should seek urgent medical attention in the event of any fever, sore throat, skin infection or rapid deterioration in general health, even in the absence of specific symptoms [11, 12].

CONCLUSION

This case illustrates an atypical, severe and misleading presentation of agranulocytosis induced by synthetic antithyroid drugs, namely extensive bullous dermohypodermitis, which can delay diagnosis and management. It highlights the importance of the judicious prescription of synthetic antithyroid drugs, strict adherence to dosage recommendations—particularly at the start of treatment—and regular clinical and laboratory monitoring. Finally, it underscores the vital role of informing patients about warning signs of infection, enabling early management and reducing the risk of serious complications.

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