

## Case Report

# Methimazole-Induced Neutropenic Gingival Ulcerations and Necrosis in a Middle-Aged Female: A Case Report with Clinical Management

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ABSTRACT

One of the major manifestations of methimazole-induced neutropenia or agranulocytosis is diffuse gingival ulceration and necrosis. The aim of this case report is to be familiar with drug-induced neutropenia and its associated oral manifestations and the healing of the gingiva after proper treatment.

**KEYWORDS:** *Antithyroid drugs, complications, hyperthyroidism, neutropenia*

## INTRODUCTION

Hyperthyroidism is a pathological disorder characterized by increased synthesis and secretion of thyroid hormone and secretion from thyroid gland. Grave's disease is the most common cause of hyperthyroidism followed by toxic nodular goiter. The mainstay of therapy of hyperthyroidism is antithyroid drug (ATD), namely propylthiouracil, thiamazole, and carbimazole, but the American Thyroid Association/American Association of Clinical Endocrinologists guidelines recommend thiamazole as the preferred drug in Graves' disease.<sup>[1]</sup> The above drugs block thyroid hormone synthesis by inhibiting thyroid peroxidase, an enzyme involved in the production of thyroxine (T4) and triiodothyronine (T3). Although these agents are generally safe, side effects in some patients limit their usefulness. Based on their degree of morbidity, side effects are classified as minor and major. Minor side effects of ATDs occur in about 5% of patients which include cutaneous eruptions, arthralgias, and gastrointestinal upset, while the common major side effect is agranulocytosis (frequency 0.1%–0.4%). Severe gingival ulceration and necrosis are the major oral manifestations of neutropenia and agranulocytosis.<sup>[2]</sup> The prevalence of hyperthyroidism increases with age and mainly affect women.

In the present case report, the patient had been taking methimazole for 3 months due to hyperthyroidism and had signs and symptoms of methimazole-induced neutropenia, the oral manifestations of which were severe gingival necrosis and several skin lesions.

## CASE REPORT

A 46-year-old woman was referred to the outpatient department of the Department of Periodontology, Subharti Dental College and Hospital, Meerut, Uttar Pradesh, complaining of generalized gingival pain and whitish deposits on gums for the last 10 days. She had been hospitalized for the last 12 days due to sore throat, fever associated with chills, swelling over nose, gingival pain, trismus, and blister over left forearm.

Her medical history revealed that she had been diagnosed with hyperthyroidism at a local clinic 3 months previously and kept on methimazole. After 2 months of methimazole use, she presented with generalized pruritus. No rash was initially noted, although 1 week later she developed deep black necrotic ulcers along with numerous oral lesions.

Extraoral examination on the day of the presentation revealed a deep black necrotic ulcer with erythematous base approximately 2 cm in diameter on the left forearm [Figure 1a], multiple pustular nodular erythematous lesions on her nose and back, approximately 1 cm in diameter with angular cheilitis [Figure 1b], while the intraoral examination showed small, discrete whitish necrotic lesions with irregular borders on the gingiva extending from the free gingival margin to the nearby

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mucogingival junction. Whitish necrotic lesions along with pseudomembrane were observed on the labial gingiva of 14, 15, 17, 25, 26, 33, 34, 35, 42, 44, and 45 [Figure 2]. Complete blood count showed agranulocytosis with white blood cell (WBC) count  $0.7 \times 10^3/\text{mm}^3$ , neutrophil count  $23 \times 10^3/\text{mm}^3$ , hemoglobin 11.7 g/dl, and platelet count  $200 \times 10^3/\text{mm}^3$  with T4 level 54.43 pmol/L. Methimazole was immediately discontinued as she was diagnosed with methimazole-induced neutropenia and ecthyma based on blood test, clinical signs and symptoms, and medical history. Intravenous antibiotic injections were continued to prevent further infections.

As the WBC count of the patient was severely lowered as a result of methimazole-induced neutropenia, biopsy of the gingival tissue was avoided.

### Management

Periodontal treatment was delayed for 1 week until the WBC count had stabilized. Initial periodontal treatment was started by dressing the lesions with hydrogen peroxide and chlorhexidine gluconate to a limited extent to irrigate the necrotic tissue and debris. Seven days after the first dental visit, the size and whiteness grade of the necrotized gingiva had decreased remarkably and reepithelialization was observed [Figure 3a].

After 15 days, when the patient was discharged from the hospital, the WBC count was increased to  $6.6 \times 10^3/\text{mm}^3$  and the next appointment was scheduled. On the second visit, scaling and root planning with 0.2% chlorhexidine

gluconate mouthwash was prescribed for its bactericidal effect.

The patient was further recalled at 3 and 6 months for follow-up.

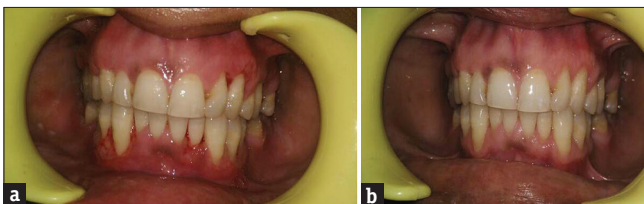
Six-month follow-up revealed that the patient was asymptomatic with no extraoral lesions and with healthy gingiva and oral mucosa [Figures 3b and 4].

### DISCUSSION

The patient in this case report was diagnosed of methimazole-induced neutropenia based on the results of clinical symptoms, medical history, and hemogram. The first line of defense against infections are neutrophils which comprise 50%–70% of the circulating WBCs. Patients with neutropenia can be categorized as mild (absolute neutrophil count [ANC] 1000–1500/ $\mu\text{l}$ ), moderate (ANC 500–1000/ $\mu\text{l}$ ), or severe (ANC <500/ $\mu\text{l}$ ).<sup>[3]</sup> The causes of acquired neutropenia include bone marrow disorders, autoimmune neutropenia, nutritional deficiencies, collagen and vascular disorders, chemotherapy, infections, and nonchemotherapy drug-induced neutropenia. Severe acute neutropenia in adults without concomitant thrombocytopenia and



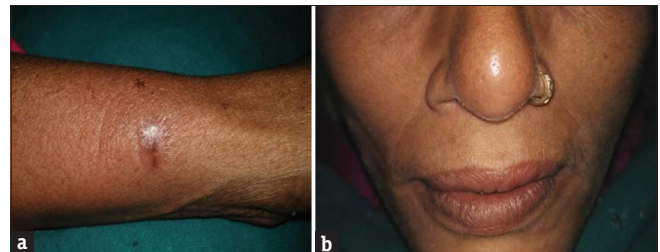
**Figure 1:** Extraoral findings at first dental visit: (a) A deep black necrotic ulcer with erythematous base seen on the left forearm. (b) Unilateral angular cheilitis on left commissures and multiple pustular nodular erythematous lesions on the nose



**Figure 3:** (a) Seven days after the first dental visit: The necrotic area decreased remarkably, and reepithelialization had started. (b) Six months after the first visit: Intraoral presentation



**Figure 2:** Intraoral findings at first dental visit: A zone of whitish necrotic lesions was found on the labial gingiva of 14, 15, 17, 25, 26, 33, 34, 35, 42, 44, and 45, extending from the free gingival margin to MGJ



**Figure 4:** Six months after the first visit: Extraoral presentation. (a) resolution of the ulcer on patient's left forearm. (b) swresolution of lesions on lips and nose

anemia is almost uniformly caused by drug-induced agranulocytosis.<sup>[4]</sup> Although the terms agranulocytosis and neutropenia are similar, agranulocytosis refers to cases with an ANC <100/ $\mu$ l. Neutrophils differentiate and proliferate in the bone marrow in about 14 days which then circulate through peripheral blood and migrate into tissues, where they survive for 1–2 days. Therefore, in circulation, the average half-life of neutrophils is about 12 h. The patient developed symptoms of neutropenia within 2 months of taking methimazole. However, patients show improvement over 2–3 weeks after discontinuing methimazole, as in the present case. The onset of methimazole-induced neutropenia is abrupt and idiosyncratic;<sup>[5]</sup> agranulocytosis usually develops within the first 2–12 weeks of ATD therapy, but can occur as late as 20 weeks after ATD therapy is initiated.<sup>[6]</sup> The mechanisms that explain why ATD-induced agranulocytosis/neutropenia develops are some drugs have the potential to be oxidized to reactive metabolites by neutrophils, thus inducing an immune response by activating inflammasomes, thus destroying neutrophil-direct toxicity.<sup>[7]</sup> Suppression of the bone marrow by methimazole is one of the causes of neutropenia in this patient. However, the patient was not taking any other drug previously and at the time of presentation, but drug-induced agranulocytosis can be caused by other drugs such as dipyron (an analgesic), ticlopidine, captopril (cardiovascular drugs), and phenytoin and azepine (anticonvulsants).

To establish a causal relationship between the drug and the adverse event, it is essential to recognize adverse drug reactions (ADRs) and temporal relationship. For the causality assessment, WHO-Uppsala Monitoring Center (UMC), Naranjo score, and preventability scale score are widely accepted. The score for the current ADR of WHO-UMC is probable/likely;<sup>[8]</sup> Naranjo score is 5,<sup>[8]</sup> preventability scale is probably preventable,<sup>[9]</sup> Table 2 and temporal relationship is highly probable.<sup>[10]</sup> Hence, the drug reaction is moderately severe.

Although neutropenia or agranulocytosis can be caused by various underlying diseases, the oral manifestations are quite similar. The pathological process of drug-induced gingival necrosis and oral ulcerations is not completely understood. It is plausible that patients with drug-induced neutropenia are vulnerable to acute opportunistic infection of putative microbiota. To palliate, some patients with sore throat and gingival pain might first visit a dentist. The various treatment challenges can be faced by dentist which are as follows:

1. Susceptibility to infections increases which results in inadequate wound healing
2. Caution should be taken while prescribing

nonsteroidal antiinflammatory drugs (NSAIDs) in the patients who have hyperthyroidism and who take  $\beta$ -blockers, as NSAIDs can decrease the efficiency of  $\beta$ -blockers

3. Increased levels of anxiety and stress are seen in patients who have hyperthyroidism and surgery can trigger a thyrotoxic crisis. Therefore, epinephrine is contraindicated, and elective dental care should be postponed.

Hence, it is crucial for the dentist to rapidly screen the patient, reach at an early differential diagnosis, give relevant recommendations, and refer patients to physicians.

There have been earlier reports of such adverse effects of ATD [Table 1].

This case is unique as the patient also presented with skin lesions. Ecthyma is a variant of impetigo that causes infiltration of bacteria over epidermis to the superficial dermis and heals with scarring.

**Table 1: Review of recent case reports of methimazole-induced neutropenia**

Authors	Year	Follow-up	Findings
Chang et al. <sup>[11]</sup>	2017	8 months	Fever, sore throat, chills, dysphagia. Numerous diffuse gingival ulcerative lesions with irregular borders in maxilla
Kim et al. <sup>[12]</sup>	2015	3 years	Sore throat, fever, and showing extensive gingival necrosis with pain in maxilla and mandible
Thomas <sup>[13]</sup>	2013	No follow-up	Fever, sore throat, and several skin lesions

**Table 2: Preventability criteria according to Schumock and Thorntorn scale**

**DEFINITELY PREVENTABLE**

1. Was there a history of allergy or previous reactions to the drug?
2. Was the drug involved inappropriate for the patient's clinical condition?
3. Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state?
4. Was a toxic serum drug concentration (or lab monitoring test) documented?
5. Was there a known treatment for the adverse drug reaction?

**PROBABLY PREVENTABLE**

6. Was required therapeutic drug monitoring or other necessary laboratory tests not performed?
7. Was a drug interaction involved in the ADR?
8. Was poor compliance involved in the ADR?
9. Were preventable measures not prescribed or administered to the patient?

**NOT PREVENTABLE**

If above all criteria not fulfilled

This patient possibly had pruritus from methimazole and when she established methimazole-induced neutropenia, her excoriations became superinfected with skin-colonizing *Staphylococcus aureus*. Treatment of ecthyma is systemic penicillin, and as expected, this patient's skin lesions dramatically improved with parenteral antibiotics.<sup>[13]</sup>

## CONCLUSION

Methimazole-induced neutropenia leads to gingival ulceration and necrosis along with systemic symptoms such as fever and sore throat in some patients. The first step to recovery includes early confirmation of methimazole's effect and early discontinuation of the drug. Chemotherapeutic methods and proper oral hygiene maintenance are important for reducing bacterial load to control the disease. Therefore, there is need for awareness of these oral complications for accurate diagnosis and for providing immediate medical intervention.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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