Extensive gingival necrosis and sequestration of the alveolar bone caused by methimazole-induced neutropenia and three-year follow-up

Eun-Cheol Kim1,4, Joon Bong Park2,3,4, Ji-Youn Hong3, Kyung Lhi Kang2,3,4,*

1Department of Oral and Maxillofacial Pathology, School of Dentistry and Research Center for Tooth & Periodontal Regeneration (MRC), Kyung Hee University, Seoul, Korea
2Department of Periodontology, School of Dentistry, Kyung Hee University, Seoul, Korea
3Department of Periodontics, Kyung Hee University Dental Hospital at Gangdong, Seoul, Korea
4Institute of Oral Biology, School of Dentistry, Kyung Hee University, Seoul, Korea

Case Report
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Purpose: Methimazole is an anti-thyroid drug that can cause life-threatening neutropenia in rare situations. The aim of this case report is to describe a set of oral complications associated with methimazole-induced neutropenia and the healing of the gingiva after proper treatment.

Methods: A 31-year-old female patient hospitalized for systemic symptoms of sore throat and fever and showing extensive gingival necrosis with pain was referred to the Department of Periodontology from the Department of Endocrinology. Methimazole-induced neutropenia was diagnosed based on blood test results and her medical history. Methimazole was discontinued and a range of treatments was administered, including the injection of granulocyte colony stimulating factor.

Results: After systemic treatment, the gingiva began to heal as the neutrophil count increased. Approximately one year later, the gingiva had returned to a normal appearance. Twenty-one months after treatment, sequestra of the alveolar bone that had broken through the gingiva were removed. Periodic supportive periodontal treatment has been continued uneventfully.

Conclusions: The oral manifestations of gingival necrosis and ulcerations, in combination with systemic symptoms such as fever and sore throat, are the critical signs presented in the early stages of drug-induced neutropenia. Therefore, dentists need to be aware of these oral complications in order to make an accurate diagnosis and to ensure that prompt medical intervention is provided.

Keywords: Complications, Hyperthyroidism, Methimazole, Neutropenia.

INTRODUCTION

Methimazole is the drug of choice for treating hyperthyroidism. This drug blocks thyroid hormone synthesis by inhibiting thyroid peroxidase, an enzyme involved in the production of thyroxine (T4) and triiodothyronine (T3). When anti-thyroid drugs (ATD) are administered, it is important to monitor the patient for any symptoms of neutropenia, such as fever and a sore throat, even though these side effects are uncommon. Methimazole-induced agranulocytosis occurs in only 0.2%–0.3% of patients [1,2]. Although this frequency is quite low, agranulocytosis may cause life-threatening complications. There are several case reports of patients with methimazole-induced agranulocytosis in the medical literature [1-5]. However, few reports have presented the oral manifestations of methimazole-induced agranulocytosis, and only one previous case report has described oral complications caused by methimazole-induced neutropenia [6]. In our case, the patient had been taking methimazole for...
three months due to hyperthyroidism and had signs and symptoms of methimazole-induced neutropenia, the oral manifestations of which were severe gingival necrosis and sequestration of the alveolar bone. As a result, our patient required a longer healing period than the patient who was described in the previous case report [6].

**CASE DESCRIPTION**

A 31-year-old female was referred to the Department of Periodontics from the Department of Endocrinology of Kyung Hee University Hospital at Gangdong, Seoul, Korea, complaining of generalized gingival pain and whitish gingival lesions. She had been hospitalized five days previously due to a sore throat, fever, and gingival pain. Intravenous antibiotic injections (1.2 g of amoxicillin/clavulanic acid and 200 mg of isepamicin sulfate, twice a day) were initiated to treat the infection.

Her past medical history revealed that she had been diagnosed with hyperthyroidism at a local clinic nine months previously and started on propylthiouracil. She had a complete blood cell count test taken every month, and the dose of propylthiouracil was decreased as her symptoms improved. However, she developed a rash and itching sensation after six months of taking propylthiouracil. Therefore, methimazole was substituted for propylthiouracil, and the patient continued taking methimazole for three months prior to admission to the hospital.

While hospitalized, she was diagnosed with methimazole-induced neutropenia based on blood test results (Table 1), clinical signs and symptoms, and her medical history. Methimazole was immediately discontinued, and intravenous antibiotic injections were continued to prevent further infections until she was discharged. Granulocyte colony stimulating factor (G-CSF; 75 µg of filgrastim, once a day) was injected subcutaneously on the second and third days of hospitalization, in order to increase the neutrophil count and reduce the recovery time [4,7]. Dexamethasone disodium phosphate (5 mg, once a day) was also injected subcutaneously on the second and third days of hospitalization for its bactericidal effect.

The patient continued taking methimazole for three months prior to admission to the hospital. As a result, our patient required a longer healing period than the patient who was described in the previous case report [6].

**Table 1. Changes of blood cell parameters over the course of the patient’s treatment, during an observation period of three weeks (cells/mm³).**

|          | WBC    | ANC   | Lymphocytes | Monocytes | Eosinophils | Basophils |
|----------|--------|-------|-------------|-----------|-------------|-----------|
| Admission day | 400    | 16    | 256         | 128       | 0           | 0         |
| The day of the first G-CSF injection | 500    | 90    | 100         | 310       | 0           | 0         |
| 1 day after the first G-CSF injection | 1,600  | 768   | 352         | 464       | 160         | 0         |
| 2 days later | 4,900  | 3,528 | 529         | 833       | 0           | 0         |
| 4 days later | 13,200 | 10,236| 1,188       | 1,452     | 0           | 0         |
| 9 days later | 6,800  | 3,808 | 1,700       | 1,088     | 0           | 0         |
| 11 days later | 6,100  | 2,593 | 2,708       | 738       | 0           | 61        |
| 19 days later | 5,300  | 3,079 | 1,728       | 456       | 5           | 32        |

WBC: white blood cell, ANC: absolute neutrophil count, G-CSF: granulocyte colony stimulating factor.
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Gingival margins (Fig. 1 C1, C2, and C3). However, the interdental spaces and exposed root surfaces were still visible. The patient reported that she was in less pain. Since the increased WBC count had stabilized, initial periodontal treatment was started and plaque control was performed at every follow-up visit. Eight weeks after the first dental visit, the gingiva had a shiny, reddish appearance, and had become more epithelialized (Fig. 2A). At that time, the patient reported that she could consume hot and spicy food. At 18 weeks of follow-up, stippling near the gingival margin was observed along with a reddish band were observed, because the gingiva was not fully keratinized (Fig. 2B). The root surfaces were almost covered, but reduced interdental spaces were still present. At nine months of follow-up, the embrasure spaces were filled with gingiva, even though calculus and plaque retention were evident (Fig. 2C). The gingiva appeared almost normal, except for a reduced red band. At the one-year follow-up visit, her maxillary and mandibular gingiva had a normal appearance (Fig. 2D), and the keratinized gingiva was repaired, extending almost to the cementoenamel junction. At a 21-month follow-up visit, sequestra of the necrotic alveolar bone were observed at the interdental gingiva of the maxillary left central incisor (Fig. 3A) and canine (Fig. 3C). The sequestra were removed through the gingiva (Fig. 3B, D, and E) and uneventful healing of the tissue occurred. At a three-year (34-month) follow-up visit, the patient showed healthy gingiva with a normal appearance, although some interdental space was still present between the maxillary central incisors (Fig. 3F).

DISCUSSION

A patient who had been taking methimazole to treat hyperthyroidism was hospitalized due to a sore throat, fever, and gingival pain. Based on the results of blood tests, clinical symptoms, and her...
The patient showed symptoms of neutropenia three months after taking methimazole. The onset of methimazole-induced neutropenia is abrupt and idiosyncratic [1]; 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 [2]. The timing of the onset of neutropenia in the present case is consistent with previous reports. The cause of neutropenia was suppression of the bone marrow by methimazole. Drug toxicity results in the decreased production of the rapidly growing progenitor cells of the marrow. The extent of marrow suppression is generally dose-related. Many other drugs can cause non-chemotherapy drug-induced agranulocytosis, such as dipyrone (an analgesic), ticlopidine and captopril (cardiovascular drugs), and phenytoin and carbamazepine (anticonvulsants) [7].

Detecting the oral manifestations of drug-induced agranulocytosis is critical for further diagnosis and treatment. Neutropenia can be a severely dangerous condition at the time of diagnosis. Therefore, routine WBC monitoring is recommended for patients taking ATD, especially during the first three months [10,11]. However, the importance of routine WBC monitoring for the early detection of ATD-induced agranulocytosis remains controversial [2]. ATD-induced agranulocytosis sometimes has a very sudden onset, and routine WBC counts, even conducted at intervals of every one or two weeks, cannot predict the appearance of all cases of ATD-induced agranulocytosis. Therefore, it is important to inform patients taking these drugs that they should be alert to the onset of symptoms such as fever, sore throat, or other infections, even when WBC counts are normal, and that they should obtain WBC counts immediately if symptoms occur [2,7].

Gingival necrosis, oral ulceration, infectious pharyngitis, and tonsillitis are the most common oropharyngeal features of drug-induced agranulocytosis [6]. These symptoms may be the first signs of neutropenia [8]. Compared to the previous report by Hou and Tsai [6], our present case showed more extensive gingival necrosis that almost covered the entire dentition, as well as a much lower WBC count, before systemic treatment was started. This report includes a description of the long-term observation of the patient over the course of three years, and suggests that alveolar bone sequestration can be associated with methimazole-induced neutropenia, because alveolar bone sequestration was found at the 21-month follow-up visit. In general, the severity of clinical signs is proportionate to the severity of agranulocytosis [6,9]. The gingival crevice is the main source of leukocytes, and the crevicular granulocytes respond to local bacterial stimuli. In neutropenic conditions, bacterial infections are not contained and progress rapidly. Thus, cells and connective tissue elements disintegrate, and rampant necrotizing gingival lesions appear in the oral cavity [8].

For oral lesions, a policresulen dressing was applied in a sextant-wise manner to the necrotic gingiva at every visit in order to exfoliate the injured cells, induce wound cleansing and reactive hyperemia in the treated area, and facilitate rapid re-epithelialization. Policresulen is a topical hemostatic and antiseptic with a highly acidic pH, which results in a marked bactericidal action on the most common pathogens as well as efficacy against Candida albicans.
The favorable effects of policresulen are attributed to its high-
ly acidic characteristics, which cause the selective coagulation of
necrotic or pathologically altered tissues while leaving healthy tis-
ues unaffected. Therefore, policresulen is used to treat infections
of the mucous membranes and eruptions on the tongue. However,
policresulen is a polycondensation product of metacresol sulfonic
acid and formaldehyde. Although no reports have yet indicated
that policresulen is carcinogetic, and the formaldehyde content is
0.36 µg per 1 mL in the Albothyl® concentrate solution, which is far
below the threshold of 0.5 mg/mL used by the registration authori-
ties in Germany according to the manufacturer, policresulen may
have potential carcinogenic effects. In addition, a 0.1% chlorhexi-
dine gluconate mouthwash was administered twice a day during
hospitalization and at home after discharge. Chlorhexidine gluco-
nate is a bactericidal agent that is effective against both Gram-
positive and Gram-negative bacteria. Hence, it is an effective anti-
plaque and antigingivitis agent that reduces gingival inflammation
[13]. After the ANC reached a normal level, the patient received
scaling and root planing.

In addition to fever and/or a sore throat, which are the best
known and typically the earliest presentations of drug-induced
neutropenia, oral manifestations, such as gingival necrosis and ul-
cerations, may be the first signs of neutropenia. Even if oral mani-
festations are not the first signs of neutropenia, their occurrence is
clinically significant. Therefore, dentists need to be aware of the
oral complications of non chemotherapy drug-induced neutropenia
in order to make an accurate diagnosis and ensure that prompt
medical intervention is provided.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was re-
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ORCID

Eun-Cheol Kim http://orcid.org/0000-0002-8445-2594
Joon Bong Park http://orcid.org/0000-0003-4959-8587
Ji-Youn Hong http://orcid.org/0000-0003-1040-7077
Kyung Lhi Kang http://orcid.org/0000-0002-0511-5742

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