

# Management of Oral Mucosal Red Lesions with Pathogenesis Considerations: Two Case Reports

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Red lesions, Hyaluronic acid, Dexamethasone, Cetirizine, Pathogenesis.

## ABSTRACT

**Introduction:** Red lesions on the oral mucosa occur due to various reasons related to the patient's condition, such as allergic reactions, autoimmune disorders, or systemic diseases. Red lesions cause pain, paresthesia, burning, or are accompanied by erosion, thus disrupting the function and comfort of the mouth. Management of red lesions varies depending on the pathogenesis of the diagnosis and systemic conditions. This case report aims to describe the management of red lesions of the oral mucosa by considering the pathogenesis of both cases.

**Case:** The first case is a 31 years old woman with a history of hyperthyroidism and is being treated thyrozol with a dose of 1x5 mg/day, while the second case is a 23 years old woman with a history of atopy. Both complained that the oral mucosa felt numb, rough, thick and stiff, accompanied by red spots. Extraoral examination revealed dry lips in both cases and the second case was accompanied by erosion. Intraoral examination showed erythematous erosions on the upper and lower labial mucosa in both cases.

**Case management:** the first case was given 0.025% hyaluronic acid mouthwash (3x10 ml/day), while the second case was given compound topical medication containing: lanolin, petroleum jelly, and dexamethasone (3-5x/day), as well as cetirizine tablet (1x10 mg/ day).

**Result:** After treatment for 1 week, both patients experienced significant improvement, and after 2 weeks the lesions in both patients had healed

**Conclusion** Management of oral mucosal red lesions that takes into considered pathogenesis factors and systemic conditions in both cases shows satisfactory results.

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## INTRODUCTION

Red lesions are among the most common types of lesions that appear on the oral mucosa. They occur due to inflammation, atrophy of the oral mucosa, dilation of blood vessels, or reduced keratinization of the oral mucosal epithelium.<sup>1,2</sup> Red lesions typically manifest as erosive or macular lesions. Erosive red lesions often cause symptoms such as burning or pain, as seen in conditions like pemphigus vulgaris and oral lichen planus<sup>3</sup>. This is due to damage to the deeper layers of the epithelium.<sup>4</sup> However, patients with macular-type red lesions often report symptoms such as itching, burning, stiffness, and gum discomfort. Reddish macular lesions are often associated with allergic reactions, Adverse Drug Reactions (ADRs), or represent lesions still in the healing process, marked by increased vascularization. Most patients present with these complaints because their quality of life has been affected.<sup>5</sup>

The incidence/prevalence of oral mucosal lesions, as reported in the study by Gaba N et al., ranges from 2% to 83% of the world's population.<sup>1</sup> The prevalence of red oral mucosal lesions, such as those seen in allergic stomatitis, reaches 70-75% of the global population<sup>6</sup>. Whereas, red macular lesions related to ADRs are relatively rare. These lesions often progress to erythema multiforme, which has an incidence rate of 20% of the global population, and Stevens-Johnson Syndrome (SJS), with an incidence of 1 per 1,000 cases per year.<sup>1,7,8</sup>

Long-term drug use and hypersensitivity reactions are among the many causes of red lesions on the oral mucosa. Prolonged drug use leads to adverse drug reactions (ADRs), which may include xerostomia, pigmentation, ulcerative lesions, vesiculobullous lesions, red or white lesions, and a burning sensation.<sup>9,10</sup> Mild ADRs category present as spot lesions or reddish macules on the oral mucosa, while more severe ADRs could result in ulcerative or vesiculobullous lesions. One drug known to cause ADRs is thyrozol, an anti-thyroid medication used for the treatment of hyperthyroidism. Thyrozol contains thiol/thionamide compounds, which provide to trigger inflammation in blood vessels, leading to an immune response that causes a reddish rash, sometimes accompanied by pain, paresthesia, and other inflammatory reactions.<sup>11-14</sup>

There are other classes of drugs that also cause oral problems such as xerostomia and burning sensation in the mouth, including beta-blockers, antidepressants, and antihypertensive drugs. Other drugs such as amlodipine and aspirin also often trigger pemphigus vulgaris and oral lichen planus. Therefore, dentists are advised to ask about the history of medication consumed by the patient.<sup>14</sup>

Hypersensitivity reactions are abnormal immune responses in the body that are excessive to substances considered dangerous, known as allergens. Gell and Coombs (1963) categorized hypersensitivity reactions into four types based on the mechanisms that cause tissue damage. Type I is a rapid reaction mediated by immunoglobulin (IgE), Type II is a cytotoxic reaction mediated by IgG/IgM, Type III is an inflammatory reaction mediated by immune complexes, and Type IV is a delayed reaction mediated by T cells.<sup>15</sup> According to the World Allergy Organization (WAO), the prevalence of hypersensitivity or allergic reactions affects 22% of the global population and is increasing every year. One common hypersensitivity reaction is allergic contact cheilitis. This condition occurs when the mucosa or skin comes into contact with an allergen, such as cosmetics, sunscreen, mouthwash, preservatives, metals, and others.<sup>16</sup> The reaction will develop from a few days to several years after exposure to the causative agent.<sup>16-18</sup>

The management of red lesions on the oral mucosa typically involves antihistamine, especially in cases of hypersensitivity reactions. If the allergen is identified, the cause of the allergy should be eliminated immediately. Red lesions of the oral mucosa related to ADRs, which are often caused by long-term drug use, require communication with the treating physician for consultation on potential adjustments to medications or dosage to reduce ADRs symptoms in the oral mucosa. In general, management of red lesions of the oral mucosa requires topical anti-inflammatory drugs which are also added with antihistamines if necessary. Management of red lesions of the oral mucosa is usually given antihistamines, especially in hypersensitivity reactions, in addition if the allergen is known, the cause of the allergy must be stopped immediately. Red lesions of the oral mucosa related to ADRs which are usually due to long-term drug use communicate with the treating doctor for consultation regarding suggestions for changing drugs or adjusting the dose to reduce ADRs symptoms in the oral mucosa. Based on theory, the management of red lesions of the oral mucosa requires topical anti-inflammatory drugs which are also added with antihistamines if necessary. Topical anti-inflammatory drugs include steroid and non-steroid, adjusted to systemic conditions and the severity of the lesion.

The availability of topical anti-inflammatory drugs in Indonesia is still limited, although both steroid and non-steroid could be drug of choice. This case report discusses the management and therapeutic considerations for two cases of red lesions on the oral mucosa with different etiologies and pathogenesis, with the aim of serving as a reference for evidence-based dental practitioners.

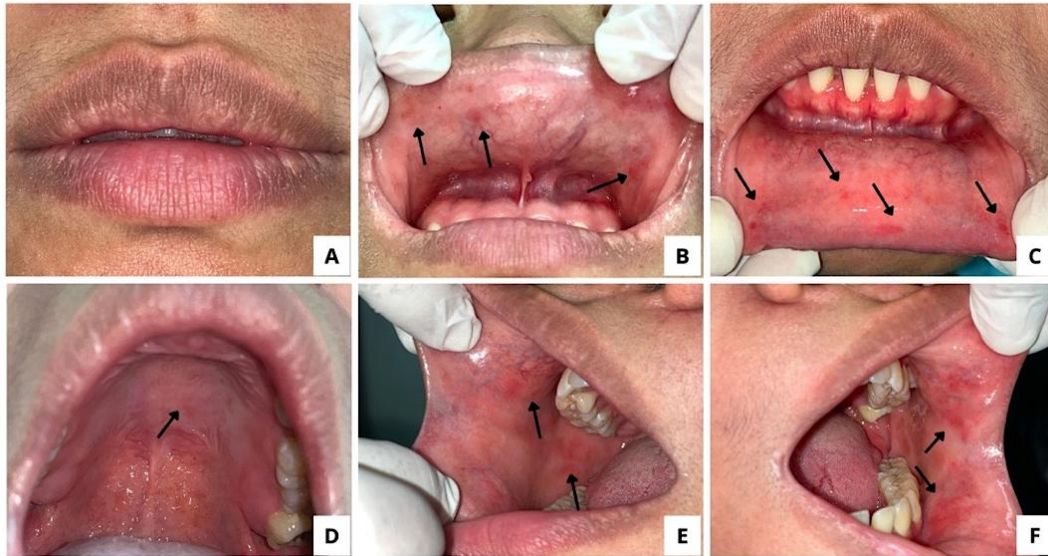
## CASE REPORT

### CASE 1

#### First visit

A 31-year-old woman came to the Padjadjaran University Dental and Oral Hospital (RSGM Unpad) with complaints of a numbness, roughness, burning sensation, taste disturbances, dry mouth, and pain when swallowing since 4 days ago. To relieve symptoms, the patient independently gargled with salt water. The patient is currently a housewife without a household assistant and in the past month the patient has felt tired. The patient has a history of hyperthyroidism and routinely consumes thyrozol 1x0.5 mg/day. The patient had experienced remission from her hyperthyroidism and the medication was stopped for 2 years, but relapsed early this year.

The extraoral examination found dry lips without exfoliation (**Figure 1A**) and lymph nodes within normal limits based on visual observation and palpation. The intraoral examination found reddish erosive lesions, multiple, with a size of about 2mm, irregular borders, found on the upper and lower labial mucosa (**Figure 1B and 1E**), right and left buccal mucosa (**Figure 1C and 1D**), and palate (**Figure 1F**). The examination of oral dryness conditions using the Clinical Oral Dryness Symptom (CODS/Challacombe scale) method found a score of 1/10, there is the mouth mirror was attached to the buccal mucosa which was categorized as mild xerostomia.

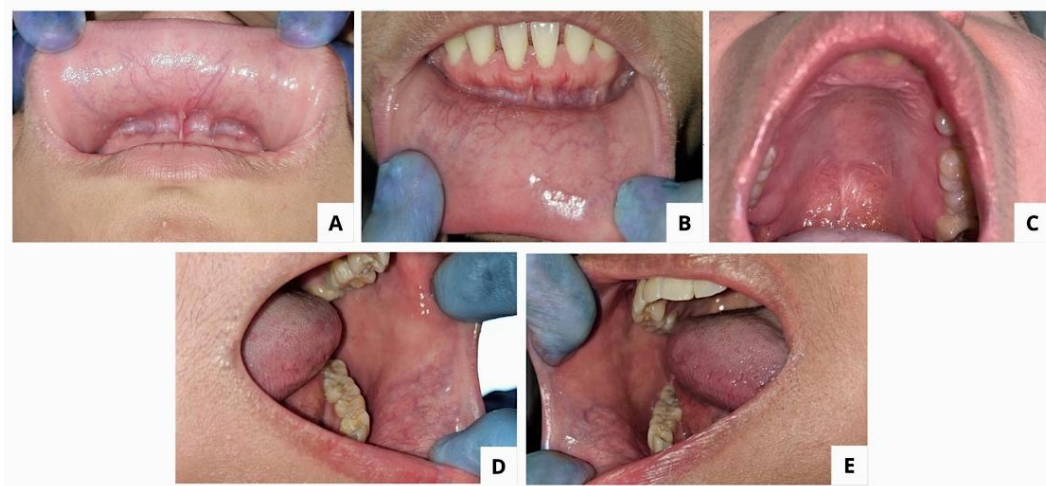


**Figure 1.** (A) Condition of the lips, (B-F) Multiple erythema on the upper and lower labial mucosa, hard palate, and right and left buccal mucosa.

The diagnosis of this patient's oral condition is ADRs stomatitis related to anti-hyperthyroidism drugs. Non-steroid anti-inflammatory drugs in the form of 0.025% hyaluronic acid mouthwash 3x10 ml/day were given to this patient. The drug was gargled for 1 minute for the oral cavity and flowed towards the throat and then discarded. The patient was also instructed to maintain oral hygiene, adequate hydration of at least 2L of water/day, and maintain a healthy balanced diet, as well as stress management as non-pharmacological therapy. The patient is advised to consult an endocrine subspecialist regarding the thyrozol drug which is suspected to be the cause of the patient's complaints.

### Second Visit

The second visit was conducted 14 days after the first visit, the patient stated that after 3 days of using 0.025% hyaluronic acid mouthwash, her complaints had improved. The dose of thyrozol for the last 7 days was also reduced by 0.5 mg/day to 0.25 mg/day after consulting with an endocrinologist. From the intraoral clinical examination, no macular/red lesions spot were found on the oral mucosa (**Figure 2A–2E**), in addition, complaints of paresthesia, pain when swallowing, and a burning sensation in the mouth had disappeared. The dry mouth condition was no longer found and the CODS score became 0/10. The patient was satisfied with the treatment given and was cooperative enough to come for a consultation with the endocrinologist who treated her. Follow-up 7 days after the second visit via WhatsApp chat, the patient stated that she did not have any symptoms. The author as the dentist who treated her said that the patient must maintain a lifestyle that includes good nutrition, hydration, sleep patterns, and stress management to prevent recurrence.



**Figure 2.** There were no red lesions/macular spots in the intraoral.

## CASE 2

### First visit

A 22-year-old female patient presented to RSGM Unpad with complaints of stiff, sore, and numb lips, along with increased redness of the lip skin for the past 4 days after using a new brand of lipstick. The symptoms began with red spots on the lips accompanied by itching, followed by the spreading of redness, causing the lips to feel stiff and thick. To relieve the symptoms, the patient used Kenalog, but this caused the lips to become drier. The patient also has a history of atopy in the form of allergic dermatitis.

On extraoral examination, the lips appeared dry and were accompanied by multiple erythematous erosive lesions with diffuse, irregular borders, variation of size, and associated with a burning sensation (**Figure 3A**). Intraoral examination revealed red macular lesions on the upper and lower labial mucosa, with diffuse irregular borders, measuring approximately 2x1 mm, and accompanied by pain (**Figures 3B and 3C**).



**Figure 3.** (A) Reddish lesions on the upper and lower lips. (B-C) Multiple erythematous lesions on the upper and lower labial mucosa.

The diagnosis of this patient is allergic contact stomatitis due to cosmetic ingredients. A topical steroid anti-inflammatory drug was given to this patient. The drug concoction consists of dexamethasone, lanolin, and petroleum jelly, which is applied to the upper and lower lips 3-5 times a day. Then the patient was given the antihistamine cetirizine 10 mg which was taken once a day for 7 days. The patient was also instructed to maintain oral hygiene and stop using lipstick which was suspected of causing the allergy.

## Second visit

Second visit after 7 days from the first visit. The patient still experienced soreness in the lips, with reddish spots remaining, but the lips were no longer stiff. **Figure 4A** shows the results of the extraoral examination: the lips appeared dry, with multiple erythematous erosive lesions having decreased, although they were still sore. The intraoral examination revealed no erythematous macules on the upper and lower labial mucosa (**Figure 4B and 4C**). The patient was instructed to continue the topical treatment with a tapering dose of once a day for 5 days, then discontinue and only apply petroleum jelly the following day. Cetirizine therapy was also stopped, and the patient was advised to return for a follow-up in one week.



**Figure 4. (A)** There is improvement in erythematous erosion lesions on the lip mucosa. (B-C) The upper and lower labial mucosa no longer has erythematous erosion lesions.

## Third visit

The 3rd visit was conducted 14 days after the first visit, the patient no longer complained of pain/stinging in the lips and oral cavity. The results of extraoral and intraoral examinations showed that the lips looked moist and there were no erythematous erosion lesions (**Figure 5A**), while the upper and lower labial mucosa also showed significant results, there were no reddish macules or stinging (**Figure 5B and 5C**). The patient admitted that he was satisfied with the treatment given, and understood the author's explanation to prevent recurrence of the disease.



**Figure 5. (A)** The lips moist without erythematous lesions. (B-C) No erythematous lesions were found on the labial mucosa.

## DISCUSSION

The lesions in both cases above show similarities, namely macular red lesions on the oral mucosa. The first case shows erythematous lesions only intraorally on the right and left buccal mucosa and the upper and

lower labial mucosa. The second case of erythematous lesions shows erythematous erosion on the lips accompanied by erythematous lesions on the lower labial mucosa. The erythematous lesions in the first case are suspected to have appeared due to the effects of ADRs of anti-thyroid drugs consumed by the patient in the last 5 years, while the erythematous lesions in the second case are suspected to have appeared due to a hypersensitivity reaction caused by lipstick.

The therapy given in the first case is a non-steroid mouthwash containing 0.025% hyaluronic acid, used 3 times a day. One of the considerations in choosing non-steroid drug therapy for patients with hyperthyroidism is based on research by Skamagas et al., which states that hyperthyroidism leads to an increase in body metabolism, indirectly affecting other endocrine systems, this provides to trigger the adrenal glands to produce cortisol more rapidly, resulting in excessive adrenal activity and potentially causing adrenal insufficiency, which leads to failure in cortisol hormone production by the adrenal glands.<sup>19</sup> Another consideration in selecting non-steroid drugs for these patients is the high level of stress they have experienced over the past few months. Stress triggers the production of cortisol, which further strains the adrenal glands to produce more of the hormone. The endocrine system is interrelated, with each hormone axis influencing the others, such as the hypothalamus-pituitary-adrenal (HPA) axis and the hypothalamus-pituitary-thyroid (HPT) axis.<sup>20–23</sup> Both of these axes are interconnected, as shown in the research by Ersantika E. et al., which indicates that increased cortisol secretion in the HPA axis provides to inhibit TSH secretion in the HPT axis, thereby increasing the risk of severe hyperthyroidism.<sup>24–26</sup>

The therapy given in the second case is a topical drug mixture containing dexamethasone, lanolin, and petroleum jelly, which is applied to the lesion 3–5 times a day, in addition to oral antihistamine tablets. Antihistamines were chosen for this therapy because the etiology is allergy.<sup>27</sup> In patients with hypersensitivity, there is an excessive production of immune cells in response to an allergen, leading to an inflammatory reaction that provides to tissue damage. Corticosteroids were selected as the therapy because corticosteroids work by suppressing the production and effects of humoral factors involved in the inflammatory response, inhibiting leukocyte migration to the site of inflammation, disrupting the function of endothelial cells, granulocytes, mast cells, and reducing T cell proliferation. Another consideration in choosing corticosteroids is that the patient does not have other systemic diseases that could be negatively affected by steroid usage.<sup>28,29</sup>

Hyperthyroidism in the first case leads to oral manifestations. Hyperthyroidism is a pathological disorder characterized by the increased synthesis and secretion of thyroid hormones by the thyroid gland.<sup>30,31</sup> The secretion and release of thyroid hormones are regulated by a negative feedback loop involving the hypothalamus, pituitary gland, and thyroid gland. The hypothalamus releases Thyroid Releasing Hormone (TRH), which activates the pituitary gland, stimulating the thyroid gland to release T4 and T3 hormones. Increased synthesis of thyroid hormones results in the inhibition of TRH and TSH release by the hypothalamus and pituitary. Disruption of this system causes excess secretion and release of thyroid hormones, leading to prolonged hyperthyroidism.<sup>32</sup> Patients with hyperthyroidism are typically treated with long-term anti-thyroid therapy, which has the potential to affect the health of the oral mucosa.<sup>11,12</sup> One potential side effect is the development of ADR symptoms, such as erythematous lesions on the oral mucosa. Other studies have also reported oral manifestations related to hyperthyroidism. According to a study by Achanta et al., patients with hyperthyroidism may experience decreased taste function, increased dental caries, and periodontal disorders.<sup>33</sup>

On the other hand, the hypersensitivity observed in the second case resulted in the appearance of erosion lesions on the lips and labial mucosa, but with a different pathogenesis. Although hypersensitivity is a part of the immune system that functions as a protective mechanism, when excessive, it leads to inflammation and damage to the body.<sup>15,34</sup> The hypersensitivity experienced by the patient falls under the category of delayed-type hypersensitivity, or type IV hypersensitivity. In this case, T cells act as the main effector cells. These sensitized T cells directly cause damage by activating other immune cells. T cells are classified into subtypes, including cytotoxic T cells and T-helper cells. These cells activated macrophages, neutrophils, and eosinophils, leading to tissue injury through the production and release of reactive oxygen species, lysosomal enzymes, and cytokines.<sup>35–37</sup> Lesions resulting from type IV hypersensitivity are not limited to erythematous erosive lesions; several other types of lesions are also possible. According to a research report by Ganesha et al., the appearance of oral mucosal lesions due to hypersensitivity reactions depends on the severity of the allergic response. These lesions range from ulcerated lesions to more severe reactions, such as anaphylactic shock.<sup>38</sup>

Anti-inflammatory drugs were administered in both cases with preparations tailored for intraoral and extraoral areas. The choice between steroid and non-steroid drugs was based on considerations of the pathogenesis and systemic conditions. In the first case, steroid mouthwash therapy could be used due to the drug's faster mechanism of action.<sup>39</sup> However, the patient has hyperthyroidism, the preferred choice was a non-steroid drug to avoid potential effects on the patient's endocrine system if swallowed. In the second case, while non-steroid drug therapy could have been used, steroid drugs were preferred because the patient presented with more pronounced clinical signs of erythema on the oral mucosa, which warranted steroid use. A compound drug preparation containing steroids was given for extraoral lesions, while for intraoral lesions, non-steroid drug therapy with 0.025% hyaluronic acid gel was applied to the lesions.

This case report has limitations, including the absence of supporting examination results that would typically be used as an ideal standard to establish the diagnosis. However, the lack of these examinations was due to time constraints and patient cost limitations. Thyroid hormone level testing could have been conducted to support the analysis of the first case's management, while an IgE examination could have been performed for the second case.<sup>40–42</sup>

In preventing recurrence of red lesions on the oral mucosa of hyperthyroidism patients by changing the type of anti-thyroid drugs could be proposed to the endocrinologist who treats the patient, in addition to maintaining a healthy diet, and training stress management. While in cases of red lesions of the oral mucosa due to hypersensitivity, to prevent recurrence could be done by consulting with an immunology specialist, conducting an IgE examination, and a skin prick test or skin test to prove a more specific allergen.

## CONCLUSION

Management of red lesions of the oral mucosa carried out by considering the pathogenesis factors of the disease and systemic conditions in both cases showed satisfactory results. Dentists are expected to be able to understand the pathogenesis and systemic conditions of patients to determine the right therapy with a better prognosis for red lesions of the oral mucosa.

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