Hypersensitivity reaction of the gingiva to chlorhexidine: case report and literature review

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Objective. The aim of this case report was to document a case of delayed-type hypersensitivity reaction of the gingiva to chlorhexidine and review the literature on oral mucosal hypersensitivity reactions associated to chlorhexidine-containing oral hygiene products.

Study Design. A 58-year-old man presented with a well-demarcated erythematous area on the right upper anterior gingiva. Incisional biopsy was performed. Postoperatively, chlorhexidine digluconate gel was prescribed twice a day, but the patient did not use it because he experienced intense burning immediately after the first application. The microscopic diagnosis was nonspecific mucositis. Hypersensitivity reaction was suspected. The patient reported use of 0.004% chlorhexidine digluconate-based toothpaste twice a day in the past few years. A delayed-type hypersensitivity reaction to the toothpaste was hypothesized, and its use was discontinued. Chlorhexidine, the common ingredient of both the toothpaste and the gel, was considered the allergen. The literature was reviewed on chlorhexidine-induced oral hypersensitivity reactions.

Results. Two weeks after cessation of toothpaste use, complete remission of the lesion was observed without additional intervention. Four years later, no recurrence has been reported. The literature review yielded 7 studies reporting 20 patients with intraoral manifestations of hypersensitivity reactions associated with chlorhexidine-containing oral hygiene products.

Conclusions. Clinicians should be aware that oral hygiene products containing even low concentrations of chlorhexidine might induce hypersensitivity reactions. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:156−160)

Hypersensitivity reactions are defined as pathologic responses produced by the normal immune system and are usually classified into 4 categories (types I−IV).[1] Type I, or immediate allergic reaction, is meditated by immunoglobulin E (IgE) antibodies and provoked by re-exposure to a specific type of antigen (allergen), such as pollen, dust mites, animal hair, drugs, and foods. It is the most common hypersensitivity reaction. Type II, or cytotoxic reaction, is characterized by deposit of IgG and IgM antibodies on the surface of host cells, causing their destruction. Common examples are autoimmune hemolytic anemia, erythroblastosis fetalis, and blood transfusion reactions. In type III reaction, deposit of antigen−antibody complexes causes damage to host cells or tissues, as is seen in several diseases (e.g., rheumatoid arthritis and systemic lupus erythematosus). Type IV, or delayed-type hypersensitivity reaction, is purely mediated by T lymphocytes, rather than by antibodies, and usually requires 1 to 2 days for the symptoms to develop. A common example is contact dermatitis that occurs after the exposure to poison oak or poison ivy.[1] A symptomatic true hypersensitivity reaction presupposes at least 1 prior asymptomatic exposure to the offending allergen, a process termed *sensitization*. Otherwise, the first contact with a triggering agent might result in a nonallergic hypersensitivity reaction, also referred to as *pseudoallergic* or *idiosyncratic reaction*.[2] Nonallergic hypersensitivity reactions, such as those caused by exposure to radio-contrast media, are mediated by mast cell activation and histamine release.[2,3]

Various substances that come in contact with the oral mucosa, such as dental materials and oral hygiene products, foods and food additives, chewing gums, and candies, may trigger acute or delayed-type hypersensitivity reactions, usually described as *allergic contact stomatitis*.[4] The clinical presentation of allergic contact stomatitis may vary: The acute form is usually associated with burning sensation, erythema, edema, and vesiculoerosive lesions, whereas the delayed-type or chronic form manifests as red and white lesions.[4] Reactions can be localized or widespread, depending on the form of the allergen.[4] The clinical and microscopic fea-

Statement of Clinical Relevance

Delayed-type hypersensitivity reactions to chlorhexidine-based toothpastes may occur, even with low chlorhexidine concentrations. Previous uneventful exposures do not preclude sudden deterioration. Clinicians should be aware of the clinical presentation of hypersensitive reactions to properly diagnose and manage them.

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tures may be diagnostic of certain allergens, that is, in contact stomatitis from artificial cinnamon flavoring or in lichenoid reactions to dental materials,[4] but in most other cases, their presence should be identified through evaluation of patient's history and elimination of other possible causative factors.[5]

Chlorhexidine, a cationic bisbiguanide with broad-spectrum bacteriostatic, bactericidal, and fungicidal activities, is broadly used as a disinfectant of skin and mucous membranes, as well as medical instruments.[6] In particular, in dentistry, it is a common ingredient of oral hygiene products, such as mouthwashes, toothpastes, gels, and lozenges.[6] Common cutaneous adverse reactions to chlorhexidine include allergic contact dermatitis or urticaria, fixed drug eruption, and photosensitivity after application of nonoral chlorhexidine-containing products, such as medications and/or cosmetics.[6,7] Cutaneous reactions have also been associated with oral sensitization by chlorhexidine-containing mouthwashes.[7-9] Rare adverse events include ototoxicity, deafness, conjunctivitis, colitis, bradycardia, anaphylaxis, or skin burns,[6,7,10] and 2 cases of fatal anaphylaxis on rinsing of an extraction socket with chlorhexidine mouthwash has also been reported.[11] In fact, on February 2, 2017, the U.S. Food and Drug Administration announced rare, but serious, allergic reactions associated with widely used chlorhexidine gluconate-containing skin antiseptic products and also emphasized the possibility of serious allergic reactions induced by chlorhexidine gluconate-based mouthwashes and oral chips used in the treatment of periodontal disease.[12]

Frequent oral adverse effects of chlorhexidine-containing oral hygiene products are discoloration of teeth, restorations, or the ventral surface of tongue; altered taste sensation; and increased calculus formation.[6,7,13,14] Allergic contact stomatitis to chlorhexidine mouthwashes has been described in the literature,[5] although poorly,[6] and its diagnosis and management may be challenging.

The aim of this case report was to describe a case of delayed-type hypersensitivity reaction of the gingiva to chlorhexidine digluconate and to review the pertinent literature on oral mucosal hypersensitivity reactions associated to chlorhexidine-containing oral hygiene products.

CASE REPORT

A 58-year-old man was referred for assessment of an asymptomatic erythematous area on the anterior maxillary gingiva, first noticed by the patient approximately 2 months before presentation. He could not recall trauma to the area or application of any particular substance on it. His medical history was noncontributory; he did not smoke, and a recent complete blood count was within normal limits.

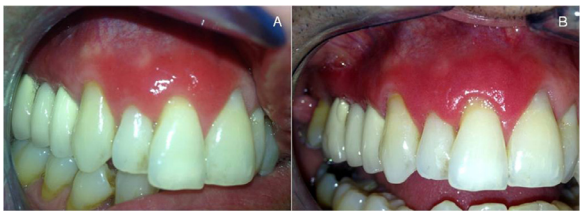

Fig. 1. **(A)** Initial examination. The free and attached gingiva in a rather well-demarcated area extending from the mesial surface of the maxillary left central incisor to the mesial surface of the right canine, are erythematous with a speckled surface. **(B)** Second examination, after 7 days. The gingival erythema had extended to the distal surface of the maxillary right first molar.

Intraoral examination revealed a well-demarcated, edematous, erythematous area, with a speckled surface involving the marginal and attached gingiva between the mesial surfaces of the maxillary left central incisor and the right canine (Figure 1A). Pain, bleeding, or desquamation was not provoked by gentle rubbing. The rest of the oral mucosa was within normal limits, and the patient's dental hygiene was very good. The differential diagnosis included plasma cell gingivitis and foreign body gingivitis.

A week after the initial examination, the erythema had extended to the distal surface of the maxillary right first molar (Figure 1B). Incisional biopsy was performed with the patient under local anesthesia. Postoperatively, application of a 0.20% chlorhexidine digluconate antiseptic gel, twice a day, was prescribed, but the patient did not use it because he experienced an intense burning sensation immediately after its first application on the area.

Microscopic examination of 5-μm thick formalin-fixed, paraffin-embedded tissue sections stained with hematoxylin and eosin showed a mucosal fragment covered by squamous epithelium. The epithelium presented hyperparakeratosis, spongiosis, acanthosis, and elongation of the rete pegs (Figure 2A), and the underlying connective tissue was vascular, with a dense inflammatory infiltrate mostly composed of lymphocytes and plasma cells in a subepithelial or perivascular distribution (Figure 2B). No periodic acid−Schiff−positive hyphae were recognized, and no birefringent foreign substance was identified by polarized light examination. The histopathologic diagnosis was nonspecific mucositis.

On further questioning, the patient reported that he had been using a 0.004% chlorhexidine digluconate−based toothpaste twice daily in the past few years. Because no other apparent allergen could be identified, a delayed-type hypersensitivity reaction to the toothpaste was hypothesized, and its use was discontinued. Complete remission of the lesion was seen 2 weeks later (Figure 3), without additional intervention. The patient was advised to avoid using chlorhexidine in any form

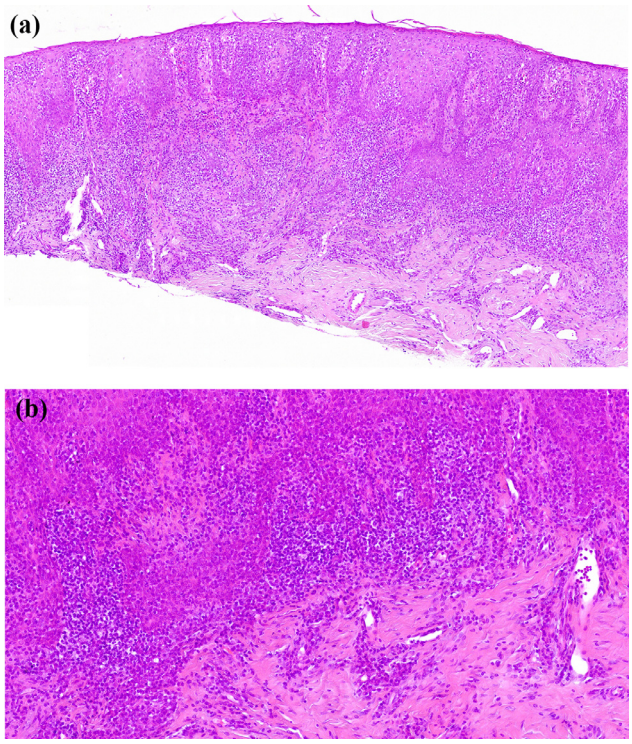

Fig. 2. Microscopic examination. **(A)** Hyperparakeratosis, elongated and anastomosing rete pegs (hematoxylin and eosin [H&E] stain; original magnification ×100). **(B)** Dense inflammatory infiltration composed mostly of lymphocytes in a subepithelial or perivascular distribution (H&E stain; original magnification ×400).

and has remained free of any sign or symptom during the 4-year follow-up period.

DISCUSSION

In the case presented here, the limited extent of the lesion and the nonspecific histopathologic features indicated an allergic or foreign body reaction to a locally applied substance. No foreign body granuloma or birefringent material was found on microscopic examination in this case. However, occasionally, the inflammatory reaction may be a nonspecific or lichenoid reaction, and the particles of the foreign material may be so small that they tend to be overlooked.[4] Desquamative gingivitis, a manifestation of lichen planus or vesiculobullous diseases, was not included in the differential diagnosis because the former typically involves additional mucosal areas, in particular, the buccal mucosa or the tongue, whereas the latter show more extensive gingival involvement and desquamation.[4]

The rapid and complete remission of the lesion after withdrawal of the 0.004% chlorhexidine digluconate–based toothpaste, as well as the intense burning sensation reported by the patient immediately after local application of 0.20% chlorhexidine digluconate antiseptic gel, supports the hypothesis that chlorhexidine, the common ingredient of both products, was the allergen.[5] A toothpaste ingredient would be expected to cause more widespread mucosal involvement, whereas in the present case, the lesion was localized. However, because it was located on a prominent side of the arch, it may be postulated that chronic improper toothbrushing technique could have caused traumatic implantation of the toothpaste in the gingival connective tissue, triggering the delayed-type hypersensitivity reaction.

Oral hypersensitivity reactions have been associated more commonly with chlorhexidine, whereas other toothpaste ingredients, such as flavoring agents, aqua, benzyl alcohol, calcium carbonate, *Chondrus crispus* (Irish moss), cellulose gum, ethylparaben, hydrated silica, limonene, lycerin, propylparaben, sodium lauryl sulfate, sodium saccharin, and titanium dioxide, have been very rarely reported as allergens.[15,16] Cases of oral hypersensitivity reaction to chlorhexidine have been described as hypersensitivity reaction,[11] allergy/contact allergy/allergic reaction,[17,18] desquamative mucosal reaction,[14] or mucosal sensitivity[19] in poorly documented reports.

Electronic databases, such as PubMed and Google Scholar, were searched for studies that included in their titles or abstracts the following key words: "Chlorhexidine AND (hypersensitivity OR allergy OR allergic OR reaction OR anaphylaxis OR anaphylactic shock) AND (oral OR buccal OR tongue OR lingual OR palate OR palatal OR

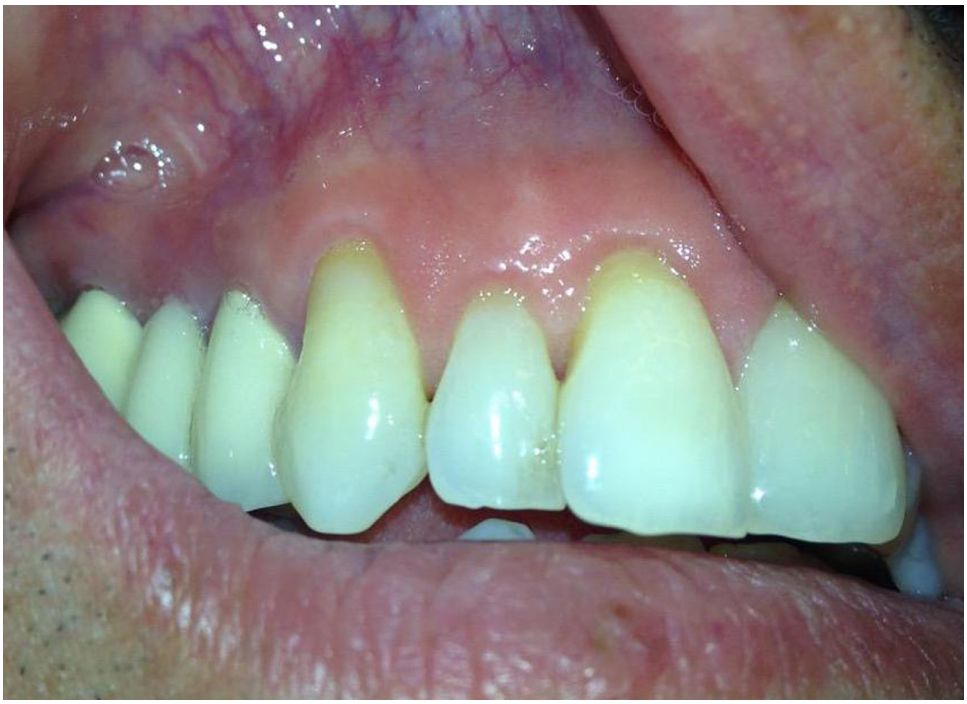

Fig. 3. Follow-up. Normal appearance of the gingiva 2 weeks after discontinuation of chlorhexidine-containing toothpaste.

lip OR labial OR floor of mouth)." The review yielded 7 studies reporting 20 cases of intraoral manifestations of hypersensitivity reactions associated with chlorhexidine-containing oral hygiene products (Supplementary Table I).[13,14,17-21] Time of appearance, clinical presentation, and location of the intraoral lesions were variable.[13,19] Oral signs and symptoms manifested a few hours[17,19] to several days or weeks[13,14,18,20] after chlorhexidine use. Signs included lip swelling; superficial mucosal necrosis with white detached patches or desquamation; and ulcers and vesicles, often accompanied by pain or burning sensation.[13,14,17-22] In most cases, 0.2% chlorhexidine gluconate–based mouthwash was the offending agent,[13,14,21] followed by 0.1% chlorhexidine acetate mouthwash[13] or chlorhexidine gel[17,20] in concentrations as low as 0.05%.[6] To the best of our knowledge, a gingival hypersensitivity reaction to such a low concentration (0.004%) of chlorhexidine has not been documented previously. Chlorhexidine has also been associated with cytotoxicity in vitro[23] and in vivo,[10] but in the present case, the clinical and histopathologic features were not consistent with a cytotoxic reaction.

The diagnosis of a hypersensitivity reaction to chlorhexidine-containing oral hygiene products is based on the spatial and temporal associations of chlorhexidine use with the development of oral lesions and their healing after its discontinuation.[13,14,19,20] The skin patch test is of limited value in mucosal lesions.[18] To our knowledge, the microscopic features of hypersensitivity reaction to chlorhexidine have not been previously described, and although they were nonspecific in the present case, they helped direct ing the diagnostic workup.

As in this case, discontinuation of chlorhexidine-containing agents is therapeutic,[13,14,19] and administration of antihistaminic drugs is recommended when intense symptoms are present.[17] Patients should subsequently refrain from using any form of chlorhexidine because re-exposure may result in new and even more severe reactions.[6,13,14,17] Previous uneventful exposures do not preclude sudden, unexpected hypersensitivity reactions.[6,7,17,18]

CONCLUSIONS

Delayed-type hypersensitivity reaction to chlorhexidine-containing toothpastes may occur, even with use of products with low concentrations of chlorhexidine. Because of the widespread use of such oral hygiene products, the prescribing practitioner should be aware of the clinical presentation of hypersensitive reactions to properly diagnose and manage them.[6,11]

REFERENCES

1. Punt J, Stranford S, Jones P, Owen JA. Kuby Immunology. 8th ed. New York: W. H. Freeman, Macmillan Learning; 2019:1050.
2. Farnam K, Chang C, Teuber S, Gershwin ME. Nonallergic drug hypersensitivity reactions. *Int Arch Allergy Immunol*. 2012;159:327-345.
3. Clement O, Webb JAW. Acute adverse reactions to contrast media: mechanisms and prevention. In: Thomsen H, Webb J, eds. *Contrast Media. Medical Radiology*, Berlin, Heidelberg, Germany: Springer; 2014:51-60.

4. Neville BW, Damm DD, Allen CM, Chi AC. Oral & Maxillofacial Pathology. 4th ed. St. Louis, MO: WB Saunders; 2016:146-148.
5. Feller L, Wood NH, Khammissa RA, Lemmer J. Review: allergic contact stomatitis. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2017;123:559-565.
6. Krautheim AB, Jermann TH, Bircher AJ. Chlorhexidine anaphylaxis: case report and review of the literature. *Contact Dermatitis*. 2004;50:113-116.
7. Moghadam BK, Drisko CL, Gier RE. Chlorhexidine mouthwash-induced fixed drug eruption. Case report and review of the literature. *Oral Surg Oral Med Oral Pathol*. 1991;71:431-434.
8. Sharma A, Chopra H. Chlorhexidine urticaria: a rare occurrence with a common mouthwash. *Indian J Dent Res*. 2009;20:377-379.
9. Watts TJ, Thursfield D, Haque R. Fixed drug eruption due to chlorhexidine mouthwash confirmed by lesional patch testing. *J Allergy Clin Immunol Pract*. 2019;7:651-652.
10. Neri I, Ravaioli GM, Faldella G, Capretti MG, Arcuri S, Patrizi A. Chlorhexidine-induced chemical burns in very low birth weight infants. *J Pediatr*. 2017;191:262-265. e262.
11. Pemberton MN, Gibson J. Chlorhexidine and hypersensitivity reactions in dentistry. *Br Dent J*. 2012;213:547-550.
12. U. S. Food and Drug Administration (FDA). Drug Safety Communication: FDA warns about rare but serious allergic reactions with the skin antiseptic chlorhexidine gluconate. Available at: https://www.fda.gov/media/102986/download. Accessed April 15, 2020.
13. Flotra L, Gjermo P, Rolla G, Waerhaug J. Side effects of chlorhexidine mouth washes. *Scand J Dent Res*. 1971;79:119-125.
14. Skoglund LA, Holst E. Desquamative mucosal reactions due to chlorhexidine gluconate. Report of 3 cases. *Int J Oral Surg*. 1982;11:380-382.
15. Sainio EL, Kanerva L. Contact allergens in toothpastes and a review of their hypersensitivity. *Contact Dermatitis*. 1995;33:100-105.
16. de Groot A. Contact allergy to (ingredients of) toothpastes. *Dermatitis*. 2017;28:95-114.
17. Keni NN, Aras MA, Chitre V. Chlorhexidine allergy due to topical application. *Indian J Dent Res*. 2012;23:674-676.
18. Liippo J, Kousa P, Lammintausta K. The relevance of chlorhexidine contact allergy. *Contact Dermatitis*. 2011;64:229-234.
19. Yusof WZ, Khoo SP. Mucosal sensitivity to chlorhexidine mouthwash. *Singapore Dent J*. 1988;13:39-40.
20. Almqvist H, Luthman J. Gingival and mucosal reactions after intensive chlorhexidine gel treatment with or without oral hygiene measures. *Scand J Dent Res*. 1988;96:557-560.
21. Yaacob H, Jalil R. An unusual hypersensitivity reaction to chlorhexidine. *J Oral Med*. 1986;41:145-146.
22. Plantinga NL, Wittekamp BHJ, Leleu K, et al. Oral mucosal adverse events with chlorhexidine 2% mouthwash in ICU. *Intensive Care Med*. 2016;42:620-621.
23. de Souza LB, de Aquino SG, de Souza PP, Hebling J, Costa CA. Cytotoxic effects of different concentrations of chlorhexidine. *Am J Dent*. 2007;20:400-404.

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APPENDIX

Table 1. Literature review on cases of intraoral hypersensitivity reactions associated with chlorhexidine-based oral hygiene products.

Reference	*Sex*	*Age**	*CHX-based product*	*Duration***	*Clinical presentation*	*Intraoral Site*	*Treatment & outcome*
Flotra et al 1971[9]	NA	NA	0.2% CHX gluconate mouthwash	11 weeks	"multiple lesions"	anterior tongue	CHX withdrawal for 1 week and then use of 0.1% CHX gluconate mouthwash; complete healing; no recurrence
	NA	NA	0.1% CHX acecate mouthwash	10 weeks	"lesions"	gingiva	CHX withdrawal for 4 days; complete healing
	NA	NA	0.2% CHX gluconate mouthwash	4 weeks	burning sensation, desquamation	lips, vestibule, gingiva	CHX withdrawal for 6 days; complete healing; recurrence after next use of 0.2 % CHX gluconate mouthwash; only few small remaining lesions after switching to 0.1 % CHX gluconate mouthwash
Skoglund & Holst 1982[10]	M	41	0.2% CHX gluconate mouthwash	5 days (2 times/ day)	well-defined and relatively superficial necrosis	labial anterior alveolar sulcus	CHX withdrawal for 5 days; complete healing; recurrence 4 days after next use of 0.2 % CHX gluconate mouthwash; mouthwash withdrawal and complete healing after few days
	M	45	0.2% CHX gluconate mouthwash	couple of weeks (4 times/day)	bleeding ulceration, desquamation	palate	CHX withdrawal for 2 weeks; complete healing
	M	24	0.2% CHX gluconate mouthwash	2 weeks (3 times/day)	ulceration	labial anterior alveolar sulcus	switching to 0.1 % CHX gluconate mouthwash, complete healing 4 weeks later
Yaacob & Jalil 1986[17]	NA	NA	0.2% CHX mouthwash	NA	acute swelling and ulcerations	lips	NA
Almqvist & Luthman 1988[16]	NA	NA	1% CHX digluconate gel	3 days (10min/ day)	white detached patches, ulcerations	buccal marginal gingiva	NA
Yusof & Khoo 1988[15]	F	41	CHX digluconate mouthwash	>24hours (once per day)	multiple ulcers	soft palate, oropharynx region, uvula	CHX discontinuation after 3 days of use, healing after 7 days
	F	30	CHX digluconate mouthwash	1 day	multiple ulcers	tongue, floor of mouth	CHX discontinuation after 2 days of use, healing after 12 days
Liippo et al 2011[14]	F	65	CHX mouthwash	NA, “earlier & current use”	“stomatitis”	“mouth”	NA
	F	65	CHX mouthwash	NA “earlier use”	“stomatitis”	“mouth”	NA
Keni et al 2012[13]	F	50	CHX gel	few hours	swelling, vesicles, burning sensation	lips	CHX gel discontinuation and antihistaminic (1 tablet twice a day); healing after 6 days
present case	M	58	0.004% CHX digluconate toothpaste	few years (2 times/ day)	erythematous area with speckled surface	right upper anterior gingiva	CHX-based toothpaste discontinuation; complete remission after 14 days

Abbreviations: CHX, chlorhexidine; NA, not available; M, male; F, female

*in years.

**between the onset of the CHX use and the initial appearance of the intraoral sign or/and symptoms.