

Gingival hypersensitivity reactions to toothpastes

A case series and scoping review

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ABSTRACT

Background. Hypersensitivity reactions to toothpastes are rare. The objective of this study was to present the authors' clinical cases in the past 10 years and perform a scoping review of gingival hypersensitivity responses to toothpastes.

Types of Studies Reviewed. The authors reviewed records of documented gingival hypersensitivity reactions to dentifrices at the Postgraduate Clinic of Oral Medicine, Complutense University, Madrid, Spain, from January 2013 through December 2022. Furthermore, the authors conducted a search in PubMed with no date limit for articles reporting these hypersensitivity responses up through October 18, 2023.

Results. Eleven cases were collected from the clinic. Eight gingival hypersensitivity reactions occurred in women, and 6 were associated with cinnamon. The most frequent lesions diagnosed were red gingiva. The discontinuation of the toothpaste led to the disappearance of the lesions. The search yielded 643 references. Thirteen articles were included in the scoping review, all of them case series and case reports, reporting 32 cases. Lesions affected middle-aged women most frequently, the most common hypersensitivity reaction was gingival redness, and the cases implicated toothpastes containing cinnamon and herbal composition.

Practical Implications. This study provides clues for diagnosing and treating hypersensitivity reactions to toothpastes, which may improve the identification, management, and reporting of these cases.

Key Words. Hypersensitivity reactions; hypersensitivity response; allergic reactions; gingiva; toothpaste; dentifrice.

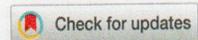
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Hypersensitivity reactions are a secondary immune response that occurs in a host with a presensitized (immune) state. In dentistry, the most common are type I and IV hypersensitivity reactions. Type I reactions are immediate and mediated by immunoglobulin E (IgE), whereas type IV are delayed and mediated by T lymphocytes. This latter form is more frequent, and it has been termed classically as contact stomatitis.^{1,2}

Toothpastes are used daily in conjunction with toothbrushing by most of the world's population. Toothpastes usually have complex formulations containing up to 20 compounds. These ingredients are not all therapeutic but contain agents to improve the toothpaste's taste, smell, texture, and preservation.^{3,4} The oral mucosal lesions that have been associated frequently with toothpastes are mostly due to irritation and hypersensitivity reactions.⁵ Toothpaste flavorings, preservatives, and fragrances have been reported as the substances most associated with contact stomatitis. Used in other cosmetic products, these agents can trigger similar reactions elsewhere in the body.⁵⁻⁸

In the United States and Europe, oral health care products are considered cosmetics. In the United States, they are regulated by the Federal Food, Drug, and Cosmetic Act and the Fair



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Packaging and Labeling Act,⁹ whereas in Europe they are regulated by European cosmetics legislation Regulation (EC) No. 1223/2009.¹⁰ Under this legislation, the requirements for toothpastes in terms of safety and biocompatibility are simpler than for drugs, and adverse effects, such as hypersensitivity reactions, are poorly reported.¹¹

Although rare, the occurrence of gingival lesions due to hypersensitivity reactions caused by dentifrices may be relevant because these products are so frequently used. For this reason, we aimed to analyze the clinical cases documented in our practice and to perform a scoping review identifying the published cases of gingival hypersensitivity reactions due to toothpastes, with the purpose of clarifying their clinical appearance and diagnosis as well as giving treatment recommendations.

METHODS

Case series

We selected all documented cases from January 2013 through December 2022 reporting gingival hypersensitivity responses to toothpastes from the records of the Postgraduate Clinic of Oral Medicine, Complutense University, Madrid, Spain. All patients provided written consent allowing their anonymized clinical records to be used for research purposes.

In all cases, the diagnoses of hypersensitivity responses to a toothpaste were confirmed after the disappearance of the gingival lesions when the toothpaste use was discontinued. In some specific cases, other diagnostic tests such as patch tests, blood tests, and biopsies also were performed.

In all cases, the patient's demographic data and reason for consultation as well as the characteristics of the lesions and composition of the toothpaste involved were collected. Other diagnostic tests (histopathology reports, patch test, or blood test) and clinical photographs as well as the treatment applied and duration of the lesions also were recorded.

Scoping review

We performed the scoping review following the Preferred Reporting Items for Systematic Review and Meta-Analyses Extension for Scoping Reviews (eTable 1, available online at the end of this article).¹²

Search Strategy

We performed a search in PubMed, with no language or publication date restriction, up through October 18, 2023. We used the following search strategy: ((oral hypersensitivity reaction) OR (oral hypersensitivity response) OR (allergic gingivitis) OR stomatitis OR (plasma cell gingivitis) OR (oral allergic reactions) OR (oral contact allergy)) AND ((toothpaste) OR (dentifrice) OR (oral hygiene products)).

Eligibility Criteria

We included articles that met the inclusion criteria: studies evaluating the occurrence of hypersensitivity responses due to toothpastes located in the gingiva; randomized or nonrandomized clinical studies, prospective or retrospective studies, case series, or clinical cases; studies published up to October 18, 2023; articles published in any language; and studies conducted in humans.

We excluded systematic reviews, literature reviews, and letters to the editor; studies that did not specify that the hypersensitivity responses were in the gingiva; studies that did not make clear the association between the toothpaste and the lesion; studies in patients with oral disorders such as oral lichen planus, pemphigus, or pemphigoid; and studies in which the hypersensitivity response was not due to toothpaste but to other oral hygiene products, such as mouthrinse or tooth powder.

Selection of Studies

Two reviewers (R.M.L.-P., K.I.S.) conducted the search independently and reviewed the titles and abstracts of all identified references. Full texts were obtained for selected studies and for those in which a clear decision could not be made on the basis of titles and abstracts alone. Any disagreement was resolved via discussion with a third reviewer (J.G.-S.). Two reviewers reviewed the full texts (R.M.L.-P., K.I.S.). Disagreements also were resolved via discussion with a third reviewer (J.G.-S.).

ABBREVIATION KEY

CHX: Chlorhexidine.

IgE: Immunoglobulin E.

NS: Not specified.

PCG: Plasma cell gingivitis.

Data Extraction

From the included studies, we extracted author, year of publication, country of origin, type of study, patients' sex and age, type of gingival lesion, onset, toothpaste ingredient associated with the hypersensitivity lesion, tests performed and results, treatment, and lesion resolution.

Statistical analysis

We carried out a descriptive analysis of the characteristics of the cases with gingival hypersensitivity response due to toothpastes, both in the case series and in the literature search. We presented continuous variables in means (SD) and categorical variables in numbers and percentages. We analyzed data using SPSS Version 28.0 (IBM).

RESULTS

Case series

Within the past 10 years, 11 cases of hypersensitivity responses affecting the gingiva associated with the use of different toothpastes were diagnosed. The characteristics of each of these cases are depicted in Table 1. Eight cases (72.7%) affected women, and 3 (27.3%) affected men. The mean (SD) age of patients was 50.09 (16.86) years (range, 14-70 years).

The most common clinical symptoms (63.6%) were itching and presence of slight pain or discomfort, mainly when toothbrushing or eating. The duration of the lesions before their diagnosis ranged from 5 days through 2 years.

Figures 1 and 2 show the photographs of the included cases. In most of the cases (81.8%), the clinical manifestation was an erythematous gingival lesion that did not respond to supragingival or subgingival instrumentation. There were 2 cases (18.2%) with necrosis in the free gingiva (Figure 1, case 2; Figure 2, case 7), and 1 case with gingival enlargement (Figure 1, case 5). Most of these gingival lesions were localized (81.8%), usually affecting the anterosuperior gingiva. Only 2 cases (18.2%) had diffuse involvement of gingival tissue (Figure 1, cases 2 and 4). In 36.4% of the patients, there were other oral mucosal lesions outside the gingiva, mainly on the tongue and lip.

The types of toothpastes associated with these lesions were varied. Six cases (54.5%) were associated with Oral B Pro-Expert (Procter & Gamble), 2 (18.2%) with Colgate Herbal (Colgate-Palmolive), and 1 with each of the following toothpastes: Gingilacer (Lacer), Perio-Aid Intensive Care gel (Dentaid), and Sensodyne Original (GlaxoSmithKline).

Patch tests were performed in 54.5% of patients, and the results were positive for various toothpaste ingredients (cinnamon, chlorhexidine, tea tree oil). Biopsies were performed in 45.5% of the patients, and they received histologic diagnoses of plasma cell gingivitis. In 2 patients (18.2%), IgE blood levels were analyzed, being high in both cases (normal range, < 100 IU/mL). Case no. 2 had levels of 215 IU/mL, and case no. 5 had values of 230 IU/mL. These 2 cases were clinically more severe than the others (Figure 1).

In all cases, the lesions disappeared after discontinuation of the offending agent (after 15 days-11 weeks). Figure 1 shows the cases in which photographic records were available before and after toothpaste discontinuation.

Scoping review

The literature search yielded 643 references. After we reviewed the titles and abstracts, we included 46 references that fulfilled the protocol criteria for full-text evaluation. Seven full texts published before 2001 could not be retrieved, even after we requested them from the authors. After this full-text review, 26 studies did not meet the criteria and were excluded (eTable 2, available online at the end of this article); hence, we included 13 studies for data analysis.^{1,13-24} The flow diagram of this search is depicted in Figure 3.

The patients in the report by Endo and Rees²² in 2007 were the same as those reported in the article by the same authors in 2006,¹⁹ so we considered these 2 studies as 1, which resulted in a total of 12 studies. Table 2 depicts the details of each of the included studies. The included studies were published from 1973 through 2023 from the following countries: India (n = 3), United States (n = 3), United Kingdom (n = 2), Greece (n = 1), Nepal (n = 1), Sweden (n = 1), and Saudi Arabia (n = 1). Nine were case reports and 3 were case series, and they included 32 documented cases of gingival hypersensitivity responses associated with the use of a toothpaste.

Table 1. Characteristics of gingival hypersensitivity response cases observed at the Postgraduate Clinic of Oral Medicine, Complutense University, Madrid Spain in the past 10 years.

CASE NO.	AGE, Y	SEX	CHIEF SYMPTOM	ONSET	CLINICAL FINDINGS	TOOTHPASTE AND COMPOSITION	TEST	TREATMENT AND RESOLUTION
1	63	Female	Red lesions and discomfort in the maxillary gingiva	3 mo ago	Gingival erythematous lesion with granular appearance from the maxillary right second premolar to the left lateral incisor; erythematous lesion on tip of the tongue.	Oral B Pro-Expert (Procter & Gamble): glycerin, hydrated silica, sodium hexametaphosphate, propylene glycol, polyethylene glycol-6, aqua, zinc lactate, sodium lauryl sulfate, aroma, sodium gluconate, <i>Chondrus crispus</i> powder, trisodium phosphate, stannous fluoride, sodium saccharin, xanthan gum, cerifera wax Copernicia, cinnamal, silica, sodium fluoride, CI [†] 77891, eugenol, CI 74160	Positive patch test for cinnamon	Disappeared 15 d after discontinuing the use of toothpaste
2	69	Female	Redness, pain, and gingival discomfort; unsuccessful previous periodontal treatment	2 y ago	Generalized lesions in free and attached gingiva. Attached gingiva was erythematous. Free gingiva had a necrotic appearance. Spontaneous gingival bleeding. The patient also had 2 ulcers, 1 on the right lateral border of the tongue and 1 on the inner side of the upper lip.	Gingilacer (Lacer): aqua, hydrogenated starch hydrolysate, hydrated silica, glycerin, propylene glycol, sodium monofluorophosphate, xylitol, aroma, titanium dioxide, xanthan gum, sodium C14-C16 olefin sulfonate, zinc chloride, sodium lauroyl sarcosinate, dipotassium glycyrrhizate, trehalose, bisabolol, sodium hydroxide, sucralose, O-cymen-5-ol	Blood tests showed immunoglobulin E levels > 100 IU/mL	Substantial improvement 15 d after stopping the use of toothpaste; total clinical resolution after 45 d
3	39	Female	Painless redness and spontaneous bleeding of the maxillary gingiva; unsuccessful previous periodontal treatment	2 mo ago	Gingival erythema of the lower one-third of the gingiva from the maxillary right canine to the maxillary left first premolar.	Oral B Pro-Expert	Positive patch test for cinnamon	Disappeared 15 d after discontinuing the use of toothpaste
4	55	Female	Maxillary and mandibular gingival redness and pain when eating; unsuccessful previous periodontal treatment	6 mo ago	Erythematous maxillary and mandibular free and attached gingivae. Generalized involvement; spontaneous bleeding.	Oral B Pro-Expert	Positive patch test for cinnamon	Disappeared 25 d after discontinuing the use of toothpaste
5	59	Male	Asymptomatic erythematous and exophytic gingival lesions; bleeding on toothbrushing; unsuccessful previous periodontal treatment	5 mo ago	Erythematous exophytic lesions with a speckled appearance on the maxillary gingiva from the maxillary right central incisor to the maxillary left first molar. Similar lesions on the gingiva of the mandibular arch from the mandibular right first premolar to the mandibular left first premolar.	Oral B Pro-Expert	Subgingival anaerobic and <i>Candida</i> cultures with negative results. Blood tests showed immunoglobulin E levels > 100 IU/mL. Positive patch test for cinnamon. Biopsy: PCG*	After discontinuation of the offending agent, improvement observed at 4 wk; resolution of the lesions 11 wk later

* PCG: Plasma cell gingivitis. † CI: Color index.

Table 1. Continued

CASE NO.	AGE, Y	SEX	CHIEF SYMPTOM	ONSET	CLINICAL FINDINGS	TOOTH PASTE AND COMPOSITION	TEST	TREATMENT AND RESOLUTION
6	34	Female	Gingival redness associated with itching; unsuccessful previous periodontal treatment	6 mo ago	Erythematous lesion affecting the free and inserted gingiva from the maxillary right canine to the maxillary left canine.	Sensodyne Original (GlaxoSmithKline): potassium nitrate, sodium fluoride w/v fluoride ion, water, sorbitol, glycerin, hydrated silica, cellulose gum, sodium methyl cocoyl taurate, silica, titanium dioxide, flavor, sodium saccharin, trisodium phosphate, red 28	Biopsy: PCG	Disappeared 25 d after discontinuing the use of toothpaste
7	55	Female	Erythematous and itching gingival lesions; patient allergic to mites and penicillin; unsuccessful previous periodontal treatment	3 mo ago	Erythematous gingival lesions on the inserted gingiva. White lesions are observed on the free gingiva. The lesions are located from the maxillary right canine to the maxillary left canine. There are also erythematous lesions on the left lateral border of the tongue.	Colgate Herbal (Colgate-Palmolive): calcium carbonate, sorbitol, silica, sodium lauryl sulphate, polyethylene glycol, sodium carboxymethyl cellulose, sodium monofluorophosphate, sodium saccharin, myrrh extract, chamomile extract, tea tree oil, sage oil, eugenol, CI 74260 in aqueous base, sodium silicate, xanthan	Biopsy: PCG	Disappeared 3 wk after discontinuing the use of toothpaste
8	70	Male	Gingival itching after scaling and root planing treatment; prescribed a toothpaste with 0.12% chlorhexidine	5 d ago	Gingival erythema from right lateral incisor to left canine affecting free and inserted gingiva.	Perio-Aid Intensive Care gel (Dentaid): chlorhexidine digluconate, CI 42090, cocamidopropyl betaine, glycerin, hydroxyethylcellulose, polyethylene glycol 40 hydrogenated beaver oil, polyethylene, sodium saccharin, xylitol, aqua, aroma	Positive patch test for chlorhexidine	Disappeared 1 wk after discontinuing the use of toothpaste
9	53	Female	Redness and spontaneous bleeding of the maxillary gingiva; unsuccessful previous periodontal treatment	3 mo ago	Gingival erythema from maxillary right canine to maxillary left lateral incisor; lesion with punctate; bleeding on probing.	Oral B Pro-Expert	Biopsy: PCG	Disappeared 15 d after discontinuation of the offending agent
10	14	Male	Patient referred by his periodontist for erythematous lesions on the gingivae of the maxillary right lateral incisors; the lesions are asymptomatic; unsuccessful previous periodontal treatment	6 mo ago	Erythematous lesions on the free gingiva of the maxillary incisors. There is also involvement of the inserted gingiva of the right incisors. Granulomatous appearance.	Oral B Pro-Expert	Biopsy: PCG	Disappeared 2 wk after discontinuation of the offending agent
11	40	Female	Erythematous gingival lesions; discomfort on the inner side of the upper lip	2 mo ago	Gingival reddening corresponding to the maxillary right premolar and maxillary right canine. She also has gingival lesions in the mandibular arch from the mandibular right canine to the mandibular left lateral incisor. Erythematous lesion on the inner face of the upper lip in contact with the maxillary right canine.	Colgate Herbal	Positive patch test for tea tree oil	Disappeared 2 wk after discontinuation of the offending agent



Figure 1. Photographic images of the cases of gingival hypersensitivity responses due to toothpastes observed at the Postgraduate Clinic of Oral Medicine from January 2013 through December 2022 (case nos. 1-5). **A.** First visit. **B.** Clinical response to the discontinuation of the offending agent. Table 1 shows the information related to each of the cases, following the same numbering for cases.



Figure 2. Photographic images of the cases of gingival hypersensitivity responses due to toothpastes observed at the Postgraduate Clinic of Oral Medicine from January 2013 through December 2022 (case nos. 6-11). Follow-up was not available in these cases. Table 1 shows the information related to each of the cases, following the same numbering for cases.

Table 2 depicts the characteristics of these 32 cases, with 25 (78.1%) being women and 7 (21.9%) men. The mean (SD) age of the affected patients was 40.72 (16.28) years (range, 17-71 years).

The most frequent clinical manifestation was the presence of reddened gingiva (26 cases, 81.3%). A smaller number of cases showed edematous ($n = 7$; 21.9%), swollen ($n = 5$; 15.6%), desquamated ($n = 5$; 15.6%), ulcerated ($n = 4$; 12.5%), speckled ($n = 3$; 9.4%), or enlarged ($n = 2$; 6.3%) gingiva. Lesions were generalized in 6 cases and localized in 4 cases, but most studies did not provide this information. Four patients had symptoms of a burning sensation (12.5%), 3 patients had pain (9.4%), and 1 patient had pruritus (3.1%). In addition, 6 patients experienced bleeding when toothbrushing (18.8%). Patients reported experiencing the lesions from 1 day through 2 years.

Associated toothpastes varied widely, but 21 cases (65.6%) were due to toothpastes containing cinnamon and 5 (21.1%) were due to toothpastes having an herbal composition. Ingredients documented as being associated with gingival hypersensitivity responses included acacia, chlorhexidine, formaldehyde, R-carvone and S-carvone, and *Salvadora persica*.

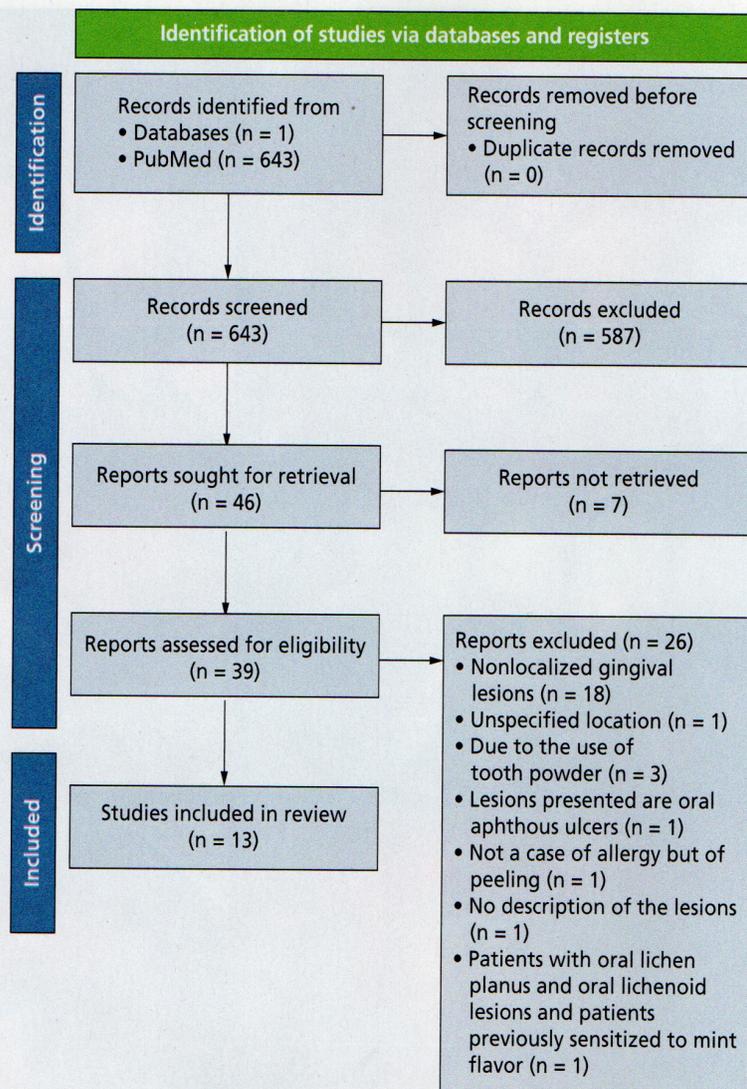


Figure 3. Flow diagram of the scoping review performed according to Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines.¹²

The most frequent diagnostic tests performed were biopsy (15 cases; 46.9%), patch tests (10 cases; 31.3%), general blood test (5 cases; 15.6%), and blood allergy test (1 case; 6.2%). In most cases (n = 31; 96.9%), treatment consisted of discontinuation of the offending agent, and in 30 of those 31 cases, the lesions disappeared. In cases for which this information was available, the lesions disappeared after 1 week through 4 weeks. Five patients also received periodontal treatment (15.7%), 2 patients (6.3%) were treated with topical corticosteroids, 1 was treated with antihistamines, and 1 underwent surgical treatment.

DISCUSSION

Our study reports the clinical characteristics, symptoms, and results from other diagnostic tests from 11 cases of documented gingival hypersensitivity responses due to the use of toothpastes. This information is supplemented with a scoping review that identified all published cases documenting these gingival reactions. Both studies showed that the occurrence of these lesions is rare. Our scoping review showed that these lesions have been documented poorly in the scientific literature, which may result in a challenge for oral health care practitioners facing the diagnosis of these lesions, given that the use of toothpaste is ubiquitous.

Dentifrices are used for oral hygiene by patients of all ages several times a day. Therefore, possible allergens in toothpastes could be in direct contact with the gingiva,^{3,25} which, in principle, could cause hypersensitivity responses in predisposed people.²⁶ However, as shown in our study, these hypersensitivity reactions are infrequent. This discrepancy could be explained by the dentifrice

being strongly diluted in water and saliva when toothbrushing. Furthermore, people usually rinse after toothbrushing, and hence the contact time with the toothpaste is short, approximately for 2 minutes 2 or 3 times per day.^{4,8}

Patients identified in our case series and in the scoping review had a mean age of 50.09 years and 40.72 years, respectively; however, patients aged 14 through 71 years were identified, which indicates that these hypersensitivity responses could affect people of all ages. These toothpaste hypersensitivity reactions were more frequent in women (>70%) than in men, which coincides with other studies reporting skin contact dermatitis occurring more frequently in women (>80% of cases).²⁷

Toothpastes contain many ingredients, including detergents, humectants, abrasives, sweeteners, fluoride, fragrances, thickeners, colorants, flavorings, antiseptics, and preservatives.^{4,5,8,25} Our case series and the studies we identified in the literature have shown that the most common allergens in toothpastes are ingredients added to improve the taste and to provide a feeling of fresher breath. The most common flavorings and fragrances added in dentifrices are menthol, spearmint, cinnamon, peppermint, carvone, and anethole.^{4,7,8,25} Among these, cinnamon has been the allergen most frequently associated with gingival lesions. In fact, this agent has been shown to be an irritant and sensitizer in high concentrations.^{4,7,8,18-20,22} Considering these facts, we would recommend that toothpastes containing cinnamon as a flavoring should be labeled properly to warn people who are highly predisposed to hypersensitivity reactions. Hypersensitivity responses to R-carvone and S-carvone also were identified in the scoping review. Carvone is found in essential oils, especially in caraway, peppermint, and dill seeds. This component is a flavoring added in toothpastes.¹⁸ Other possible allergens present in toothpastes are fragrances,¹¹ such as tea tree, which is an essential oil,⁴ and its presence was identified in the toothpaste used in 1 of the patients from our case series.

Other possible agents associated with gingival hypersensitivity responses include chlorhexidine, which is mainly used as a mouthrinse rather than in a toothpaste formulation and was identified in 1 patient from our case series and has been described in another study.¹ Hypersensitivity responses to other plants or herbal compounds also were identified, such as *Salvadora persica*, a shrub commonly known as toothbrush tree that contains benzyl isothiocyanate.¹⁵ Another case was associated to acacia, a tree used for medicinal and preservative purposes that contains pollen and hence may cause allergic reactions.¹⁶ Triclosan is an antimicrobial chemical that also is used in health care-related products. There are published cases of contact dermatitis associated with this compound.²⁸ However, we could not identify any cases associated with this ingredient in our review and in our service. Perhaps the failure to find hypersensitivity reactions to this compound is because of the 2017 US Food and Drug Administration statement that obliged cosmetic companies to go through a special control when products contain this compound and made it mandatory that the compound appear in the list of ingredients. This is due to the fact that a certain relationship was observed between long-term exposure to this ingredient and an increased risk of oral cancer.^{28,29} This may have led companies to eliminate this ingredient from the composition of oral hygiene products. Another case was associated with formaldehyde. This ingredient in toothpastes has a fungicidal, germicidal, and disinfectant action, and it acts as a preservative.²³ There were certain cases, however, in which the ingredients of the toothpastes were unknown because the labeling on the toothpastes only referred to an herbal composition. Considering this, it should be advisable to oblige manufacturers to describe the composition of the toothpastes correctly.

Oral lesions associated with hypersensitivity contact responses are diverse, including cheilitis, lichenoid reactions, and presence of erythema, edema, swelling, ulcerations, blisters, and vesicles.^{1,26} In our case series, the most frequently observed clinical lesion in the gingiva was reddened, sometimes associated with edema, swelling, desquamation, ulceration, and gingival enlargement. In all the patients described from our case series, the erythematous lesions never extended beyond the mucogingival line. This finding may be important in the differential diagnosis with other oral disorders. In 81.8% of the cases, the involvement was localized in the anterosuperior gingiva. And other associated oral lesions on the tongue and lips were observed in only 36.4% of the cases in our case series. Although the toothpaste should be spread in the entire mouth, the preferential involvement of the gingiva may be due to the fact that the toothpaste usually comes into direct contact with the gingiva several times a day. However, the rest of the oral mucosa only receives traces of toothpaste diluted in saliva or water. This has been supported by Andersen⁸ and de Groot.⁴ Likewise, other authors have suggested that perhaps an aggressive or inadequate long-term toothbrushing technique focusing in this area may facilitate these hypersensitivity reactions.¹ Normally,

Table 2. Characteristics and results of the included studies in the scoping review.

AUTHORS, YEAR	COUNTRY	TYPE OF STUDY	AGE, Y	SEX	TYPE OF LESION
Millard, ²⁴ 1973	United Kingdom	Case series (n = 3); only 1 caused by toothpaste and affected the gingiva	36	Male	Swollen and sore gingiva
Duffin and Cowan, ²³ 1985	United Kingdom	Case report	64	Male	Ulceration of the gingiva from maxillary right canine to maxillary left canine and buccal surface of the lip and swelling of the upper lip
DeLatre, ²¹ 1999	United States	Case report	27	Female	Slight free-gingival-margin erythema in the absence of plaque in the mandibular left premolar and molar region
Endo and Rees, ^{19,22} 2006 and 2007	United States	Case series (n = 37); only 19 caused by toothpaste and affected the gingiva	65, 62, 39, 42, 26, 29, 71, 27, 27, 59, 54, 54, 49, 53, 36, 65, 64, 32, 20	Female, n = 17; male, n = 2	Erythematous gingiva (n = 17); desquamation (n = 5); ulceration (n = 3); granular surface of the gingiva (n = 2); edematous gingiva (n = 2); gingival enlargement (n = 1)
Anil, ²⁰ 2007	Saudi Arabia	Case series (n = 3)	27, 26, 36	Female, n = 2; male, n = 1	Case 1: red and swollen gingiva ranging from the free gingival margin to the mucogingival junction in both arches Case 2: generalized gingival inflammation with intensely erythematous, friable, and edematous gingiva, which was more profound in the maxillary and mandibular anterior gingiva Case 3: moderate to severe inflammation of the maxillary and mandibular gingiva extending to the first molar area
Hansson and Colleagues, ¹⁸ 2011	Sweden	Case report	33	Male	History of swelling of lips and gingiva and shortness of breath
Lamdari and Pradhan, ¹⁷ 2012	Nepal	Case report	29	Female	Red and swollen gingiva, bad breath, and bleeding from gingiva during toothbrushing; severe inflammation of the gingival tissues from the free gingival margin to the mucogingival junction in both arches; negative Nikolsky sign
Makkar and Colleagues, ¹⁶ 2013	India	Case report	17	Female	Severe diffuse gingival enlargement of both dental arches; gingiva was bright red and friable, fibrous as well as edematous in consistency
Chaubal and Colleagues, ¹⁵ 2017	India	Case report	28	Female	Gingival pruritus and erythema after toothbrushing with a toothpaste containing <i>Salvadora persica</i> ; location not specified
Kotsailidi and Colleagues, ¹ 2020	Greece	Case report	58	Male	Well-demarcated, edematous, erythematous area, with a speckled surface involving the marginal and attached gingiva between teeth nos. 6 and 9
Ketkar and Kaarthikeyan, ¹⁴ 2021	India	Case report	24	Female	Painless reddish pink gingiva, which easily bled on mild provocation; desquamative surface changes
Cornelius Timothy and Colleagues, ¹³ 2023	United States	Case report	24	Female	Generalized gingival erythema and edema

* NS: Not specified. † PCG: Plasma cell gingivitis. ‡ CHX: Chlorhexidine.

Table 2. (Continued)

ONSET	RELATED TOOTHPASTE OR INGREDIENT	TEST	TREATMENT	RESOLUTION OF THE LESION
NS*	Toothpaste containing sorbitol-glycerin mix as humectant with refined silica as the abrasive; the main flavoring agents were cinnamon and menthol	Patch tests with the toothpaste ingredients: positive reaction to 0.5% cinnamon oil in petrolatum	Discontinuation of the offending agent	Total resolution after 1 wk
1 d	Desensitizing toothpaste with 1.3% formalin	Patch test: strong positive reaction to a 1% aqueous solution of formaldehyde	Discontinuation of the toothpaste; aureomycin mouthrinse was prescribed to control secondary-infection; treatment with chlorpheniramine maleate	Total resolution after 3 d
NS	Tartar toothpaste	No	Discontinuation of the tartar toothpaste	Resolution after discontinuation of the offending agent
NS	Cinnamon-flavored toothpaste	Biopsy (n = 8); patch test (n = 6)	Discontinuation of cinnamon-containing toothpaste in all cases	Total resolution in all cases
NS	Cases 1 and 2: herbal toothpaste Case 3: herbal toothpaste containing cinnamon	Biopsies (n = 2): results of PCG†	Discontinuation of the offending agent and periodontal treatment	Resolution after discontinuation of the offending agent
6 mo	Toothpaste with R-carvone and S-carvone	Open testing and patch testing for: benzoic acid, salicylic acid, citric acid, peppermint oil Brand A, peppermint oil Brand B, eucalyptus oil, R-limonene, S-limonene, R-carvone, S-carvone	Discontinuation of the toothpaste containing R-carvone and S-carvone; use a toothpaste with a fruit taste and avoid spearmint gum and spearmint sweets	Resolution after discontinuation of the offending agent
1 y	Herbal toothpaste, composition NS	Biopsy: result of PCG	Scaling, root planing, and oral hygiene with no total response; elimination of the use of toothpaste resulted in the disappearance of the lesions	Resolution 4 wk after discontinuation of the offending agent
2 y	Toothpaste containing Acacia (Babool; Dabur Oral Care Products)	Biopsy: result of PCG. Blood test for allergy of toothpaste components. High level of allergen specific antibody in relation for Acacia	Discontinuation of the toothpaste	Resolution 2 wk after toothpaste removal
48 h	Toothpaste containing <i>Salvadora persica</i>	Patch testing positive to <i>Salvadora persica</i>	Discontinuation of the toothpaste; use of 0.05% fluocinonide 3 times daily for 2 wk	Resolution after discontinuation of the offending agent
2 mo	0.004% CHX [‡] digluconate-based toothpaste	Biopsy: result of nonspecific mucositis	Treatment with CHX 0.20%; patient experienced an intense burning sensation and reported the use of 0.004% CHX toothpaste; discontinuation of the CHX toothpaste	After removing the toothpaste with CHX, the lesions disappeared.
4 mo	Herbal toothpaste, composition NS	Biopsy: result of PCG	Periodontal therapy and CHX 0.2% mouthrinse, no response	Resolution after discontinuation of the offending agent
NS	Herbal toothpaste, composition NS	Biopsy: result of PCG	Discontinuation of the offending agent; use of dexamethasone mouthrinse	Total resolution after treatment

the patient tends to brush only the teeth and part of the gingiva. This could explain the gingival appearance, because in other locations there is no direct relationship between the trauma of the toothbrush, the toothpaste, and the oral epithelium.

The reported symptomatology in the scoping review cases was rather scarce, with only a few cases reporting burning, slight pain, pruritic sensation, and bleeding on toothbrushing.^{15,17,24} The most consistent symptom in our case series was a slight pain or discomfort associated with itching in 63.6% of the patients, mainly when toothbrushing or eating. This scarcity of symptoms makes the diagnosis of these gingival hypersensitivity responses challenging for the dentist.²⁶ The differential diagnosis should be made with cases of desquamative gingivitis associated with oral lichen planus, pemphigus, or pemphigoid. However, people experiencing gingival hypersensitivity responses to toothpaste components do not have white reticular or plaque lesions, which are common in oral lichen planus. Also, patients do not report blistering typical of cicatricial pemphigoid or pemphigus vulgaris.^{26,30-32} Crohn disease, ulcerative colitis, or sarcoidosis also should be considered in the differential diagnosis. To rule them out, laboratory tests or a chest radiograph in the case of sarcoidosis should be requested.²² Lupus and HIV also should be considered in the differential diagnosis. Erythematous gingival lesions such as gingivitis, red macules, and telangiectasias have been observed in patients with lupus.³³ Also, HIV-positive patients may have linear gingival erythema and Kaposi sarcoma, which cause erythematous gingival lesions.^{34,35} At first these lesions also may be misdiagnosed as plaque-induced gingivitis or periodontitis,²² but these diagnoses should be discarded in light of nonresponsiveness to periodontal treatment.

In the diagnosis of these lesions, it is important to obtain a medical history, including not only past diseases but also a comprehensive drug history.¹ It should include family and personal history of allergy, atopy, and occurrence of rash in the skin as well as the presence of oral habits such as use of chewing gum, consumption of candies, and use of lipstick.²² Furthermore, a detailed reporting on the usage of oral hygiene products should allow the dentist to search for possible allergens. The chronology of the product's use in relation to the appearance of the lesions is also relevant. A history of dental treatments is also relevant in relation to the appearance of the lesion, given that cases of lichenoid reactions have been associated with dental materials with similar clinical presentation.⁶

In certain cases of a more complex differential diagnosis, it may be necessary to request complementary tests. Specifically, patch tests to identify the allergen were performed in 31% of the cases reported in our scoping review and in 55% in our case series. In these situations, it is important to know the toothpaste formulation to identify the possible allergens to test.⁶ However, in certain cases of the scoping review, the compounds to be tested were not available, so toothpaste was used as the allergen, which may result in false-positive reactions.^{4,25} If requesting a blood test, it is important to obtain a complete blood test including IgE level.¹⁷ A result of increased IgE levels may indicate the presence of hypersensitivity type 1. However, there is controversy about the normal limits. The reference value for total IgE (1.5-144 IU/mL) has been established in the literature, but this value can vary according to variables (age, sex, race, tobacco use) as well as exposure to environmental pollutants and disorders other than hypersensitivity reactions (parasitic infections, immunodeficiencies, rheumatologic diseases, cancer). Elevated levels even may be present in healthy people.³⁶ The 2 patients with elevated IgE levels in our case series were not smokers, and neither had a history of systemic diseases that could influence IgE values. However, given the chronicity of the lesions, we cannot affirm that these were type 1 or IgE-mediated hypersensitivity reactions.

In our study, the most frequent finding in the biopsies was plasma cell gingivitis. Plasma cell gingivitis is a benign inflammatory condition that histologically shows dense plasma cells that infiltrate the connective tissue. The etiology of plasma cell gingivitis is unclear, but due to the presence of plasma cells, it is thought to be an immunologic reaction to allergens.¹⁷ Plasma cell gingivitis must be differentiated from a variety of gingival lesions associated with diseases such as leukemia, multiple myeloma, or IgG4-related disease.^{22,25,37,38} The differential diagnosis is made through hematologic and serologic testing.^{14,20}

The simplest and most frequently performed treatment was discontinuation of the offending agent. This treatment was performed in 96.9% of the cases in the scoping review and in 100% of our cases. The response to the change of toothpaste was effective in 30 of 31 cases of the scoping review and in 100% of our cases. In certain cases, we changed the toothpaste for another one with fewer irritants (such as a toothpaste for xerostomia), or we simply asked the patient not to brush with toothpaste for 15 days. When the dentifrice is removed, the disappearance of the lesions may occur

after 1 week or 2 weeks, but in severe cases with ulceration and gingival enlargement, total improvement may occur later (Figure 1, cases 2 and 5). However, in our scoping review, periodontal treatment also was performed in 15.7% of the cases, topical corticosteroids were applied in 6.3% of the cases, and antihistamines were used in 1 patient. These medical treatments are useful to eliminate the symptoms and improve the lesions, but if the toothpaste is not eliminated, the cases tend to recur once the active treatment is withdrawn.

Our study has some limitations. The studies included in the scoping review were of low methodological quality. The randomized clinical trials reviewed in the initial screening did not report any adverse effects of this type. Perhaps this is due to the short duration of treatment in these studies. Because the studies were case series and case reports, there was no uniformity with respect to the variables collected. Therefore, not all the variables selected were collected in all the studies. We believe that this should be improved in the future. We believe that our study reflects the clinical picture of these gingival hypersensitivity responses as well as the diagnosis and treatment. The photographs in our case series also may help oral health care professionals in the differential diagnosis of new cases. Our report also has illustrated that certain toothpaste components such as cinnamon may behave as allergens, and hence a printed warning on the label should note that there is a potential for oral hypersensitivity. Similarly, we believe that the safety and adverse effects of toothpaste ingredients deserve further investigation by manufacturers in the future, always under the supervision of the government in the country of product origin.

CONCLUSIONS

Gingival hypersensitivity responses due to toothpaste are rare. These reactions are more common in women than in men and can appear at any age. The most frequently implicated agents in toothpastes are flavorings such as cinnamon and fragrances. As in previous studies, we also observed that the most common lesion is gingival redness that does not respond to periodontal treatment. These gingival lesions are difficult to diagnose. In the diagnosis, it is important to obtain a complete clinical history that considers the oral hygiene products used by the patient. In some cases, the patch test and biopsy also can be helpful for differential diagnosis. The removal of the involved toothpaste may result in the elimination of the lesions. It is necessary to report these gingival hypersensitivity responses to toothpaste components because the identification and replacement of these ingredients may help in their prevention. ■

DISCLOSURES

None of the authors reported any disclosures.

SUPPLEMENTAL DATA

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1. Kotsalidi EA, Kalogirou EM, Michelogiannakis D, Vlachodimitropoulos D, Tosios KI. Hypersensitivity reaction of the gingiva to chlorhexidine: case report and literature review. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2020; 130(2):156-160.e1.
2. Jutel M, Agache I, Zemelka-Wiacek M, et al. Nomenclature of allergic diseases and hypersensitivity reactions: adapted to modern needs—an EAACI position paper. *Allergy*. 2023;78(11):2851-2874. <https://doi.org/10.1111/all.15889>
3. Rahielah Kasi S, Özcan M, Feilzer AJ. Side effects of sodium lauryl sulfate applied in toothpastes: a scoping review. *Am J Dent*. 2022;35(2):84-88.
4. de Groot A. Contact allergy to (ingredients of) toothpastes. *Dermatitis*. 2017;28(2):95-114.
5. Sainio E-L, Kanerva L. Contact allergens in toothpastes and a review of their hypersensitivity. *Contact Dermatitis*. 1995;33:100-105.
6. Lavy Y, Slodownik D, Trattner A, Ingber A. Toothpaste allergy as a cause of cheilitis in Israeli patients. *Dermatitis*. 2009;20(2):95-98.
7. Otto S, Zirwas MJ. Toothpaste allergy: diagnosis and management. *J Clin Aesthet Dermatol*. 2010;3(5):42-47.
8. Andersen KE. Contact allergy to toothpaste flavors. *Contact Dermatitis*. 1978;4(4):195-198.
9. FDA authority over cosmetics: how cosmetics are not FDA-approved, but are FDA-regulated. US Food and Drug Administration. Accessed August 29, 2023. <https://www.fda.gov/cosmetics/cosmetics-laws-regulations/fda-authority-over-cosmetics-how-cosmetics-are-not-fda-approved-are-fda-regulated>
10. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products. *EUR-Lex*. August 16. Accessed August 29, 2023. <https://eur-lex.europa.eu/eli/reg/2009/1223/2019-08-13>
11. Couteau C, Morin T, Diarra H, Coiffard L. Influence of cosmetic type and distribution channel on the presence of regulated fragrance allergens: study of 2044 commercial products. *Clin Rev Allergy Immunol*. 2020; 59(1):101-108.
12. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. 2018;169(7):467-473.
13. Cornelius Timothius CJ, Stern I, Stern JK, Abdel-sayed RA, Peacock ME. Plasma cell gingivitis: clinical and pathological case report. *Compend Contin Edu Dent*. 2023; 44(5):e1-e4.
14. Ketkar GN, Kaarthikeyan G. An atypical presentation of plasma cell gingivitis with generalized skin lesions. *J Oral Maxillofac Pathol*. 2021;25(suppl 1):S54-S57.
15. Chaubal TV, Bapat RA, Bapat PR. Allergic contact stomatitis caused *Salvadora persica* in toothpaste. *Contact Dermatitis*. 2017;77(5):325-326.
16. Makkar A, Tewari S, Kishor K, Kataria S. An unusual clinical presentation of plasma cell gingivitis related to "Acacia" containing herbal toothpaste. *J Indian Soc Periodontol*. 2013;17(4):527-530.
17. Lamdari N, Pradhan S. Plasma cell gingivitis: a case report. *J Nepal Med Assoc*. 2012;52(186):85-87.
18. Hansson C, Bergendorff O, Wallengren J. Contact urticaria caused by carvone in toothpaste. *Contact Dermatitis*. 2011;65(6):362-364.
19. Endo H, Rees T. Clinical features of cinnamon-induced contact stomatitis. *Compendium*. 2006;27(7): 403-410.
20. Anil S. Plasma cell gingivitis among herbal toothpaste users: a report of three cases. *J Contemp Dent Pract*. 2007;8(4):60-66.
21. DeLattre VF. Factors contributing to adverse soft tissue reactions due to the use of tartar control toothpastes: report of a case and literature review. *J Periodontol*. 1999; 70(7):803-807.
22. Endo H, Rees T. Cinnamon products as a possible etiologic factor in orofacial granulomatosis. *Medicina Oral Patología Oral Cirugía Bucal*. 2007;12(6):E440-E444.
23. Duffin P, Cowan GC. An allergic reaction to toothpaste. *J Irish Dent Assoc*. 1985;32(3):11-12.
24. Millard LG. Contact sensitivity to toothpaste. *BMJ*. 1973;1(5854):676.
25. He W, Hu X, Hua H, Li K, Zhang C, Wei P. Allergic contact stomatitis due to desensitizing toothpastes. *J Dermatol*. 2022;49(6):648-651.
26. Larsen KR, Johansen JD, Reibel J, Zachariae C, Pedersen AML. Symptomatic oral lesions may be associated with contact allergy to substances in oral hygiene products. *Clin Oral Investig*. 2017;21(8):2543-2551.
27. Belluco PES, Giavina-Bianchi P, Belluco RZF, Novaes MRCG, Reis CMS. Prospective study of consecutive patch testing in patients with contact dermatitis using an adapted Latin American baseline series. *Eur Ann Allergy Clin Immunol*. 2023;55(5):235-242.
28. Campbell L, Zirwas MJ. Triclosan. *Dermatitis*. 2006; 17(4):204-207.
29. Szychowski KA, Skora B, Bar M, Piechowiak T. Triclosan (TCS) affects the level of DNA methylation in the human oral squamous cell carcinoma (SCC-15) cell line in a nontoxic concentration. *Biomed Pharmacother*. 2022;149:112815.
30. Saccucci M, Di Carlo G, Bossù M, et al. Autoimmune diseases and their manifestations on oral cavity: diagnosis and clinical management. *J Immunol Res*. 2018; 6061825. <https://doi.org/10.1155/2018/6061825>
31. Sciubba JJ. Autoimmune oral mucosal diseases: clinical, etiologic, diagnostic, and treatment considerations. *Dent Clin North Am*. 2011;55(1):89-103.
32. Schifter M, Yeoh SC, Coleman H, Georgiou A. Oral mucosal diseases: the inflammatory dermatoses. *Aust Dent J*. 2010;55(suppl 1):23-38.
33. Del Barrio-Diaz P, Reyes-Vivanco C, Cifuentes-Mutinelli M, Manriquez J, Vera-Kellet C. Association between oral lesions and disease activity in lupus erythematosus. *J Eur Acad Dermatol Venereol*. 2020;34(2):349-356.
34. Lombardi N, Varoni EM, Moneghini L, Lodi G. Gingival multilobulated growing-mass in HIV-positive patient. *Oral Dis*. 2023. <https://doi.org/10.1111/odi.14676>. Published online July 30.
35. Goncalves LS, Goncalves BM, Fontes TV. Periodontal disease in HIV-infected adults in the HAART era: clinical, immunological, and microbiological aspects. *Arch Oral Biol*. 2013;58(10):1385-1396.
36. Carosso A, Bugiani M, Migliore E, Anto JM, DeMarco R. Reference values of total serum IgE and their significance in the diagnosis of allergy in young European adults. *Int Arch Allergy Immunol*. 2007;142(3):230-238.
37. Zhang J, Zhao L, Zhou J, Dong W, Wu Y. Immunoglobulin G4-related periodontitis: case report and review of the literature. *BMC Oral Health*. 2021;21(1):279.
38. Goyal A, Rathore M, Singh SK, Nada R. Generalised gingival enlargement as a sole manifestation of IgG4-related disease. *BMJ Case Rep*. 2020;13(7):e236338.