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SPECIAL ISSUE: COLORS AND TEXTURES, A REVIEW OF ORAL MUCOSAL ENTITIES

Frictional Keratosis, Contact Keratosis and Smokeless Tobacco Keratosis: Features of Reactive White Lesions of the Oral Mucosa

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Abstract
White lesions of the oral cavity are quite common and can have a variety of etiologies, both benign and malignant. Although the vast majority of publications focus on leukoplakia and other potentially malignant lesions, most oral lesions that appear white are benign. This review will focus exclusively on reactive white oral lesions. Included in the discussion are frictional keratoses, irritant contact stomatitis, and smokeless tobacco keratoses. Leukoedema and hereditary genodermatoses that may enter in the clinical differential diagnoses of frictional keratoses including white sponge nevus and hereditary benign intraepithelial dyskeratosis will be reviewed. Many products can result in contact stomatitis. Dentrifice-related stomatitis, contact reactions to amalgam and cinnamon can cause keratotic lesions. Each of these lesions have microscopic findings that can assist in patient management.

Keywords Leukoplakia · Frictional keratosis · Smokeless tobacco keratosis · Stomatitis · Leukoedema · Cinnamon

Introduction

Oral leukoplakia, the most common oral potentially malignant disorder (OPMD), is defined by the 2017 World Health Organization (WHO) as "white plaques of questionable risk, once other specific conditions and other OPMDs have been ruled out." [1] This review will focus exclusively on "other specific conditions": reactive oral white lesions that have a distinct etiology rather than OPMDs. In the 2005 WHO section of epithelial precursor lesions, squamous cell hyperplasia was considered a precursor lesion and thus, termed leukoplakia [2]. In the recent WHO (2017), squamous cell hyperplasia has been omitted as an OPMD [1]. Most of these lesions are incidental findings and relate to a variety of causes including parafunctional habits, mechanical friction, contact reactions, chemical-related changes, and tobacco-related changes [2–5]. Numerous papers have been published on the clinical and histologic features of oral leukoplakia and will not be repeated herein. Inflammatory etiologies of oral white lesions including infective and non-infective causes will be discussed elsewhere in this special issue.

Frictional Keratosis

Parafunctional habits whereby there is constant rubbing, chewing or sucking of the oral mucosa against the teeth can result in keratoses of the buccal mucosa (morsicatio buccarum), tongue (morsicatio linguarum) and lip [5]. The true prevalence of frictional keratoses is unknown as studies that review oral mucosal lesions are generally clinically based and may miscategorize leukoplakia as frictional keratoses or vice versa. In some published series in children and adolescents the reported range is 0.26–5.3% [5]. Woo and Lin reviewed the histopathologic diagnosis of 584 cases of clinical leukoplakia and reported that cases related to frictional keratoses were in patients in the fifth and sixth decade [6]. The clinical appearance can vary depending on the degree of trauma. Linea alba is the term used to describe the white keratotic line on the buccal mucosa approximating the occlusal plane. Linea alba can present unilateral or bilateral and varies in color intensity and thickness [4, 5]. The surface can feel rough with irregular tags which initiates a cycle of a patient removing the rough tags with their teeth only to produce more tags. In some patients the frictional keratoses can

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be extensive involving the entire cheek and extending to the lips. These lesions will resolve upon cessation of the habit. The clinical findings can be of an ill-defined area of gray or white papules and plaques and may be associated with erosions and ulcers if the bite trauma is extensive. The affected area may exhibit a macerated appearance with shredded keratin and peeling (Fig. 1a). Generally, the clinical findings are adequate in determining the etiology of the white lesions and do not require confirmatory biopsy. However, there are instances where the etiology is unknown, or the keratotic lesion is in a high-risk area for OPMDs. This is particularly true when the lesion presents on the lateral border of the tongue, which is the most common location for oral cavity squamous cell carcinoma [7]. Therefore, it is prudent to sample any questionable lesion to rule out OPMD.

The histologic features of frictional keratosis from the tongue, lip or buccal mucosa vary slightly depending on the site of the biopsy. With few exceptions, marked hyperparakeratosis with a shaggy or shredded keratin surface is noted (Fig. 1b). Corresponding to the clinical presentation, the surface keratin can have a macerated appearance with fissures and clefting [6, 8]. Bacteria is usually present on the keratin surface in biopsies from the tongue, but not as often on the buccal mucosa or lip. Although candidal hyphae may be present this is uncommon and unrelated to the underlying etiology. The epithelium exhibits epithelial hyperplasia and intracellular edema is common presenting as ballooned cells in the spinous layer. Generally, there is a lack of inflammation in the superficial connective tissue with the exception of cases where secondary ulceration is present. In these instances, normal mitotic figures may be present in the basal or parabasal layer, but the features of epithelial dysplasia are absent.

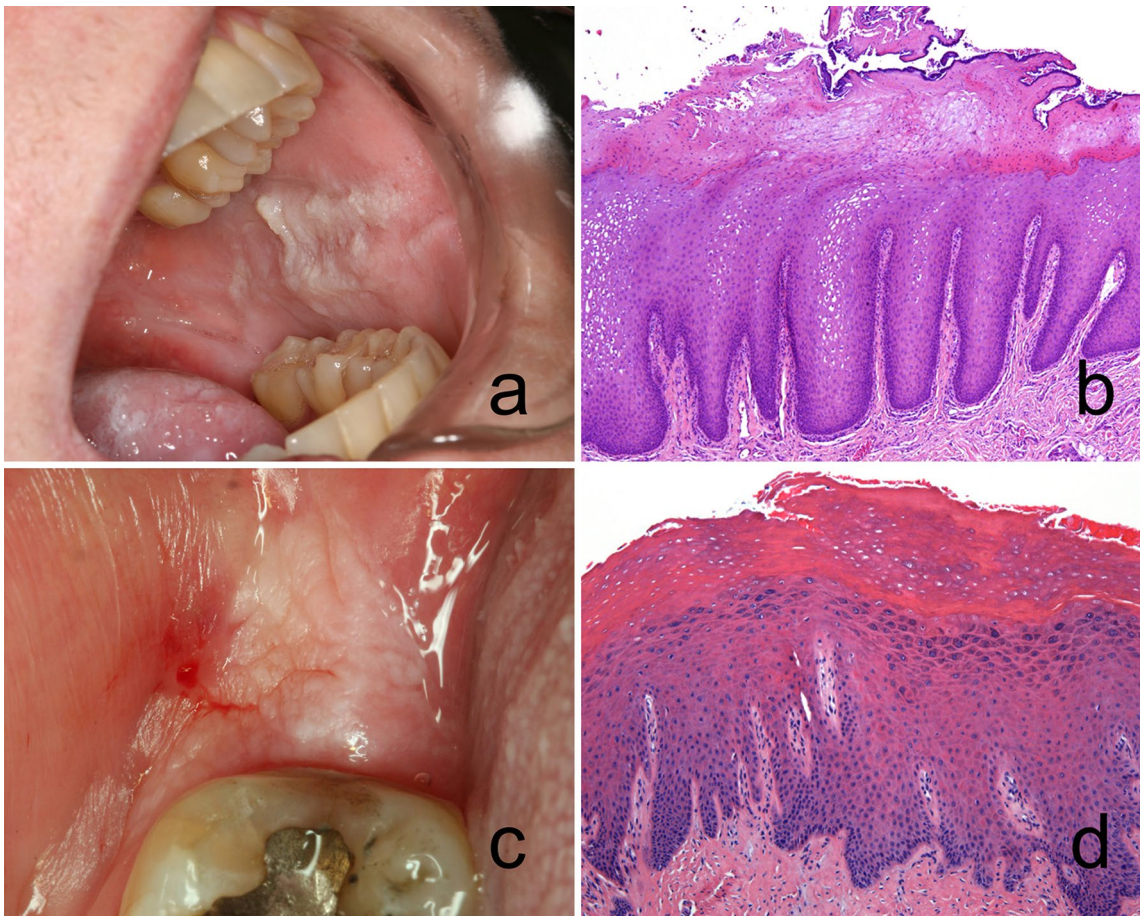

Fig. 1 **a** Irregular, shaggy macerated appearance of the left buccal mucosa typical for cheek biting (morsicatio mucosae). **b** Photomicrograph showing marked hyperparakeratosis with a shaggy appearance with surface fissures and clefts. The epithelium is acanthotic with ballooned cells. Bacterial colonies are present on the keratin surface without an inflammatory response (H&E, magnification × 100). **c** Alveolar ridge keratosis presenting as a relatively discrete keratotic plaque on the retromolar pad. This is in contrast to the diffuse, ill-defined keratotic plaques seen in proliferative verrucous leukoplakia (Fig. 2a). **d** Histopathologic features of ridge keratosis characterized by marked hyperorthokeratosis, hypergranulosis and acanthosis. The epithelium has elongated anastomosing rete. Note the lack of inflammation (H&E, magnification × 100)

The retromolar pad and edentulous alveolar ridge can exhibit benign keratosis as the area is susceptible to both masticatory forces, occlusal trauma or ill-fitting dentures or other dental appliances (Fig. 1c) [9, 10]. Frictional keratosis from the alveolar ridge usually is surfaced by orthokeratin with a slightly irregular or corrugated architecture (Fig. 1d). A prominent granular cell layer is noted. The epithelium may show acanthosis and epithelial rete may be elongated or atrophic [9, 10]. Similar to frictional keratosis of the buccal mucosa and tongue, a paucity of inflammatory cells is present. Although some authors have likened keratosis of the alveolar ridge to cutaneous lichen simplex chronicus and emphasize that these benign keratoses should be removed from the category of leukoplakia, this viewpoint is not universally accepted [9]. Care should be made in rendering a diagnosis of frictional keratosis of the alveolar ridge and more importantly, gingiva in tooth-bearing areas when limited clinical information is available. Toothbrush trauma is often cited as the etiology of keratotic lesions of the gingiva. However, most traumatized gingiva of the tooth bearing area expresses as erythema, ulceration, or other reactive lesions such as pyogenic granuloma. The clinical findings are critical in helping to distinguish between reactive keratosis and OPMD. There is both clinical and histologic overlap in the features of benign keratosis and keratosis associated with proliferative verrucous leukoplakia (PVL) which is a recognized OPMD (Fig. 2a) [8, 10]. Of unknown etiology, PVL is associated with high recurrence and malignant transformation rates. The gingiva is the most common site for PVL and in a 2014 systematic review of PVL, the gingiva was the most common site for malignant transformation [11]. PVL lesions histologically can have a varied appearance and usually corresponds to the clinical appearance. Early PVL lesions from the alveolar ridge and gingiva are indistinguishable from benign keratosis and leukoplakia without dysplasia exhibiting marked orthokeratosis with a slight corrugated surface and prominent granular cell layer (Fig. 2b) [8, 12]. In one study evaluating benign alveolar ridge keratosis with lesions exhibiting dysplasia, lesional size was not a predictor [10]. Without appropriate clinical information these lesions should be diagnosed not as frictional keratoses but as keratoses without dysplasia or as keratosis of unknown significance [13].

In addition to PVL there are benign conditions that can have clinical overlap with frictional keratosis. Leukoedema is a common, asymptomatic buccal mucosal finding of unknown etiology and is considered to represent a normal variation [4, 5, 14]. It is more common in African-Americans than in white Americans occurring in 49% of African-Americans and in 4% of white Americans in one survey of 13,000 patients [15]. This study found no sex predilection although other studies have reported leukoedema is more commonly seen in males [4]. Leukoedema affects the bilateral buccal and labial mucosa and appears as an opalescent, filmy gray to white lesion that characteristically diminishes upon stretching of the mucosa (Fig. 3a, b). This feature distinguishes leukoedema from frictional keratosis, lichen planus and leukoplakia. Although leukoedema is generally not biopsied, histologic findings of parakeratosis and spongiosis is seen [15].

Two rare genodermatoses that can have clinical overlap with frictional keratoses but have distinct histologic features are white sponge nevus (WSN) and hereditary benign intraepithelial dyskeratosis (HBID). WSN is inherited as an autosomal dominant trait that presents as asymptomatic thickened soft white plaques most commonly on the buccal

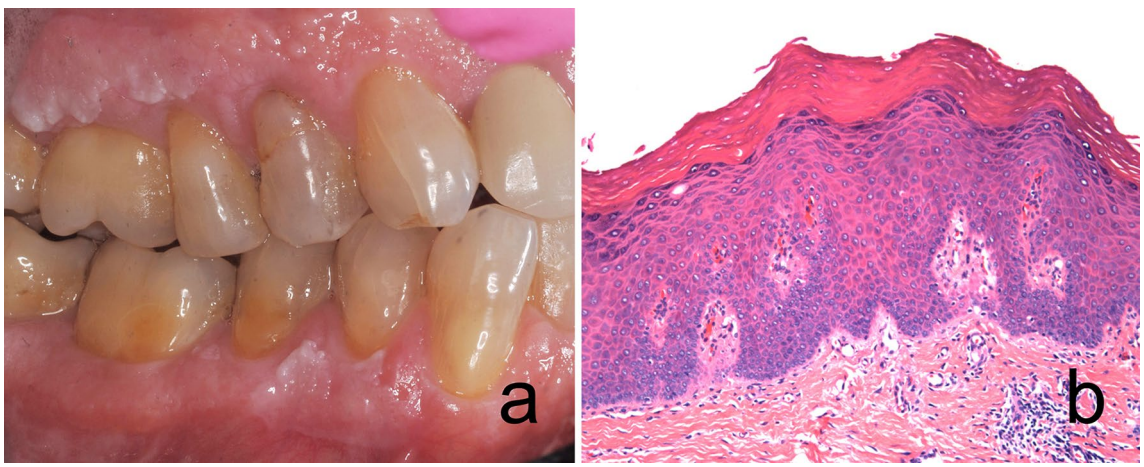

Fig. 2 **a** Clinical features of proliferative verrucous leukoplakia in a 76-year-old non-smoking female. White, thickened plaques with irregular, rough surface change are noted on the gingiva of the right maxilla and mandible. **b** Biopsy shows a corrugated or slightly papillary epithelial architecture with hyperorthokeratosis, a prominent granular cell layer but normal epithelial maturation. This histology is virtually indistinguishable from ridge keratosis (Fig. 1d) and requires clinical correlation (H&E, magnification × 100)

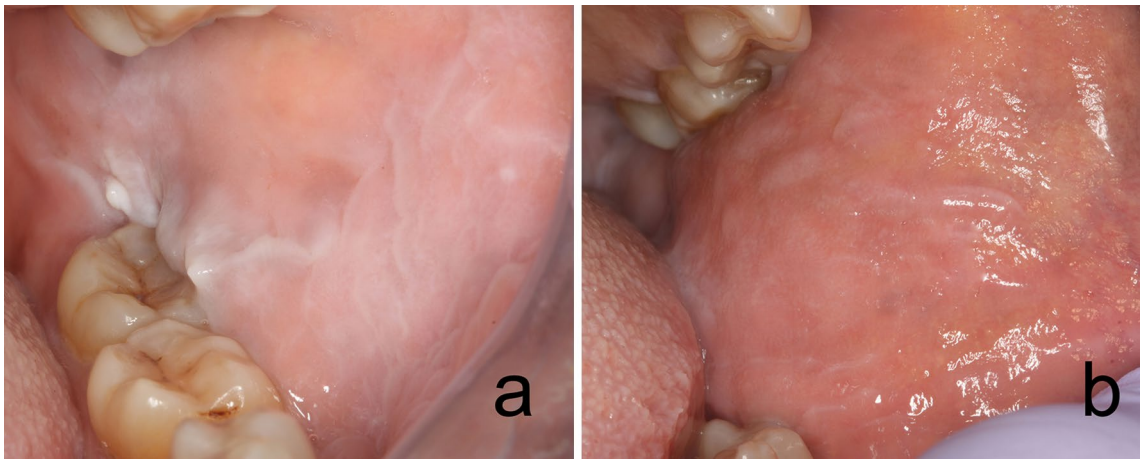

Fig. 3 **a** Leukoedema of the left buccal mucosa in a 58-year-old Black female presenting as an ill-defined opalescent filmy gray to white lesion. **b** When the cheek is everted and stretched the lesion diminishes. (Photographs courtesy of Dr. Kristin K. McNamara)

mucosa (Fig. 4a) [14, 16]. Other mucosal sites of involvement include nasal, esophageal and anogenital. Generally, first noted in childhood, the lesions wax and wane over time [14, 16]. Histologic features of WSN are distinct with prominent parakeratosis and acanthosis and clearing of the spinous cell layer (Fig. 4b). In the superficial epithelium, eosinophilic perinuclear condensation, representing compact aggregates of keratin tonofilaments, unique to WSN, is present [16, 17]. This finding can be best appreciated on exfoliative cytology with Papanicolaou staining (Fig. 4b inset).

HBID is a rare autosomal dominant disorder initially described in the tri-racial Native American tribe in North Carolina [18]. Similar to WSN, HBID presents as white spongy plaques on the buccal mucosa and tongue, but in addition, HBID has ocular findings of white gelatinous conjunctival plaques [19]. These plaques are moveable over the underlying tissue. Epibulbar blood vessels can be hyperemic resulting in a bloodshot appearance. HBID does not affect the anogenital region, esophagus or nasal mucosa. HBID is characterized histopathologically by hyperplastic stratified squamous epithelium with marked parakeratosis and acanthosis (Fig. 5). Within the parakeratin and spinous layer, are dyskeratotic cells with crenated or pyknotic nuclei surrounded by homogenously dense eosinophilic cytoplasm

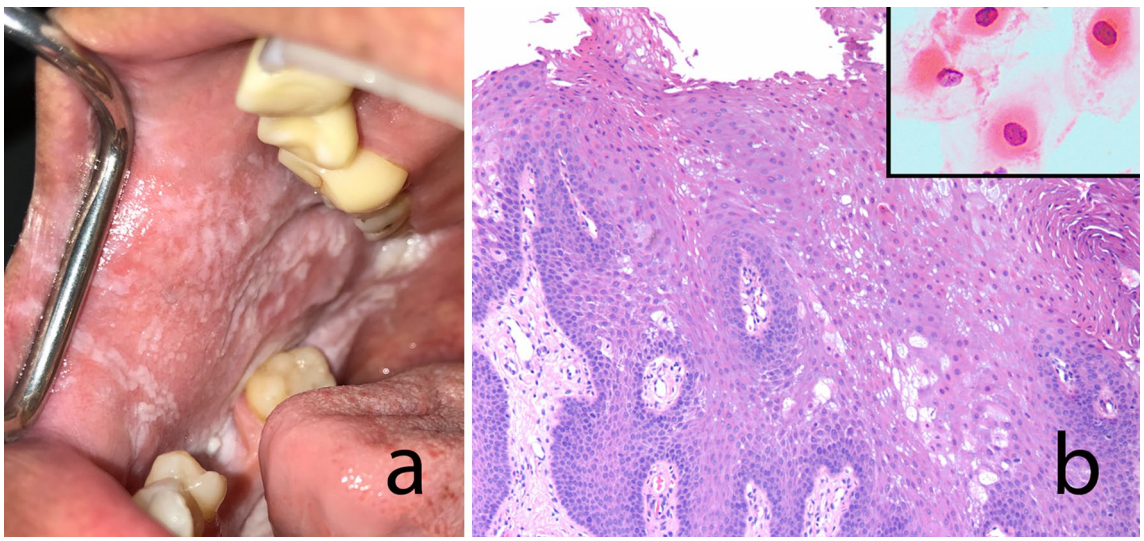

Fig. 4 **a** White sponge nevus of the right buccal mucosa in a 36-year-old Black man. Although there are clinical similarities to frictional keratoses the histology is distinct. **b** Photomicrograph of white sponge nevus exhibiting prominent hyperparakeratosis and acanthosis with vacuolation of the spinous cell layer. Within the spinous layer occasional cells with bright eosinophilic perinuclear condensation representing keratin tonofilaments can be observed. (H&E magnification × 100). Inset: High-power photomicrograph of exfoliative cytology with Papanicolaou staining demonstrating the eosinophilic perinuclear condensation (magnification × 400)

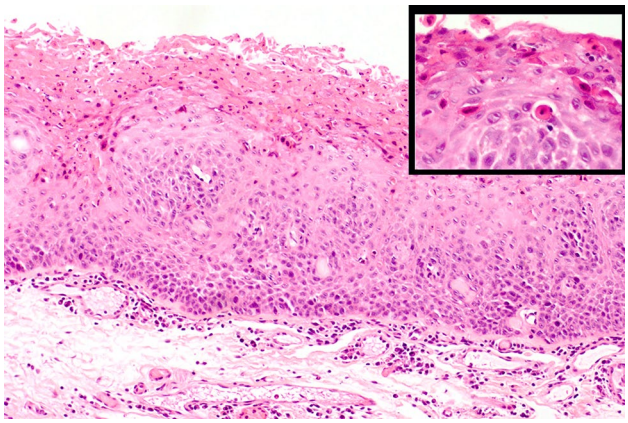

Fig. 5 Hereditary benign intraepithelial dyskeratosis. Low-power photomicrograph exhibiting marked parakeratosis and acanthosis. Scattered throughout the epithelium but most appreciated in the upper spinous layer are dyskeratotic cells. A mild lymphoplasmacytic infiltrate in the subepithelial lamina propria is typical. Inset: High-power photomicrograph highlights the dyskeratotic cells which have crenated or pyknotic nuclei surrounded by dense hypereosinophilic cytoplasm giving the appearance of intraepithelial dyskeratosis. (H&E magnification × 400). (Photographs courtesy of Dr. Hans Grossniklaus)

(Fig. 5 inset). This feature can be appreciated on cytologic preparations with Papanicolaou staining [18, 19].

Irritant Contact-Related Keratosis

The oral mucosa is exposed to a wide variety of external irritants. Irritant contact stomatitis caused by chemical products used in toothpastes, mouthwashes, and dental restorations can result in oral mucosal injury. Much of the time the oral mucosa is in contact with these products for short periods of time or saliva dilutes and buffers the irritants reducing the potential for an adverse reaction. However, with increased concentration, duration, or frequency of the chemical the patient may have a reaction and develop keratoses, ulcerations, vesicles, erythema, edema or a combination of these. Although the clinical presentation of irritant contact stomatitis share similarities with allergic contact stomatitis, patch testing is negative [20]. Three contact-related lesions that can present as white or keratotic oral lesions which have a unique histology are contact reactions to ingredients in some toothpaste, amalgam, and cinnamon flavoring agents.

In some individuals certain dentifrices can result in superficial sloughing of the oral mucosa (Fig. 6a). The buccal mucosa and vestibule are usually affected, and the appearance is of white strings easily removed with a finger without leaving any ulceration or erythema [21–25]. Ingredients associated with superficial mucosal desquamation are sodium lauryl sulfate (SLS), triclosan and tetrasodium and/or tetrapotassium pyrophosphate [21, 22]. SLS is a common synthetic detergent added to toothpaste for foaming and cleaning. Both triclosan, an antimicrobial agent, and sodium pyrophosphate are added to toothpaste either as a single ingredient or combined in tartar-control toothpaste to prevent plaque development. In addition to these ingredients, flavoring agents are added to mask the bitter taste of pyrophosphate. The exact prevalence is unknown but most likely these reactions are uncommon. Clinicians may be concerned for a vesiculo-bullous process such as mucous membrane pemphigoid. Biopsies of affected mucosa however rule out vesiculo-bullous disease, as the histology shows acanthosis

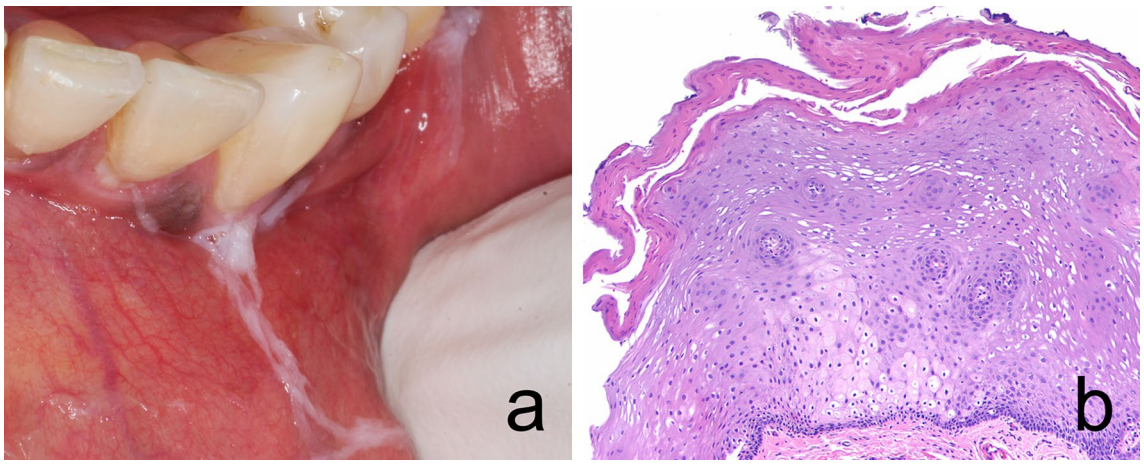

Fig. 6 **a** Superficial sloughing of the oral mucosa due to the use of triclosan and pyrophosphate containing toothpaste. There is peeling of the superficial keratin without any underlying erythema or erosion. Total resolution of the condition was achieved upon discontinuation of the tartar control toothpaste. **b** Photomicrograph demonstrates marked parakeratosis, acanthosis and intracellular edema. Intraepithelial linear clefting of the superficial parakeratin is seen. At times the superficial parakeratin is completely detached from the underlying stratified squamous epithelium or this superficial sloughing is all that is submitted for histologic examination. (H&E magnification × 100)

and intracellular edema of the stratum spinosum. Clefting of the superficial parakeratin is seen and often this superficial layer of keratin is detached from the epithelium (Fig. 6b) [24]. The connective tissue is uninflamed. These microscopic features are not unique to dentifrice stomatitis, but with appropriate clinical information, an association can be proffered. The lesions resolve after discontinuing the suspected product.

Oral contact lesions to amalgam dental restorations can present as a keratotic or lichenoid lesion (Fig. 7-1a) [8, 12, 26]. Amalgam reactions are generally considered type IV hypersensitivity reactions [26]. The lesions usually present on the buccal mucosa or tongue where prolonged contact of the mucosa with the amalgam occur. In one study, 19% of patch test positive patients to amalgam-related allergens had complete resolution after amalgam replacement and 61.5% had a partial resolution [27]. Amalgam contact reactions have clinical overlap with oral lichen planus, but unlike lichen planus, contact reactions to amalgam are usually single and can resolve upon amalgam removal [8, 12]. Admittedly there is histologic overlap with oral lichen planus and amalgam contact reactions however some microscopic findings may favor a contact reaction (Fig. 7-1b) [26, 28]. Histologically, amalgam contact reactions can have tertiary lymphoid follicle formation composed of B-cells containing follicular dendritic cells surrounded by T-cells and macrophages similar to normal tonsils (Fig. 7-1c) [29]. Another histologic feature present in amalgam contact reactions and not a typical finding in oral lichen planus is the presence of a deep inflammatory infiltrate rather than inflammation confined to the lamina propria subjacent to the epithelial basal cells. Other findings include a mixed inflammatory infiltrate, including eosinophils, and focal perivascular inflammation [28, 29].

Cinnamon flavoring agents including cinnamic aldehyde, cinnamic acid and cinnamon oil, can cause a contact stomatitis [30]. Cinnamon is used a wide array of products such as toothpaste, mouthwash, gum, candy and soft drinks. Most cases of cinnamon stomatitis are associated with prolonged contact of the offending agent. The clinical presentation can vary. Superficial sloughing of the mucosa as described above with edema and erythema of the gingiva is associated with cinnamon containing toothpaste [30]. Shaggy hyperkeratotic oral lesions are usually seen in cinnamon stomatitis from gums and candy (Fig. 7-2a) [30, 31]. Erythema and ulceration may be present. These clinical features may mimic frictional keratoses from cheek or tongue biting, however the histology is distinct from frictional keratoses. Representative biopsies show epithelial acanthosis, often with elongated rete ridges (Fig. 7-2b). Marked hyperkeratosis, either orthokeratosis or parakeratosis and neutrophilic exocytosis is present. Interface mucositis is identified, and the superficial connective tissue contains a predominately lymphocytic band-like inflammatory cell infiltrate which includes plasma cells, histiocytes and scattered eosinophils (Fig. 7-2c) [10, 31]. Perivascular inflammation composed of lymphocytes and plasma cells are observed in the deeper lamina propria.

Smokeless Tobacco Keratosis

The use of oral tobacco products used in North American and Europe can result in clinical changes at the site of tobacco placement. Termed snuff dipper's lesion, snuff pouch and spit tobacco keratosis among other terms, smokeless tobacco keratosis (STK) is the keratotic changes in the oral mucosa where smokeless tobacco product is placed [32]. Swedish-type moist snuff is termed snus and is typically placed under the upper or lower lip [33]. In North American, moist smokeless tobacco is usually placed in the lower buccal vestibule or chewed if chewing tobacco is used. Products with strong and independent risk factors for oral cancer prevalent in Southeast Asia such as betel quid, gutka, paan and others, some which do not contain tobacco will not be discussed here [34].

The thickened layer of keratin that develops where the smokeless tobacco is placed varies in clinical appearance depending on frequency of use or the amount used [35]. Early lesions tend to have a filmy white to gray opalescent appearance with a wrinkled surface and minimal mucosal thickening (Fig. 8a) [32, 35]. With progression the lesions become more keratotic with furrowing of the epithelium and thickening (Fig. 8b). The histological findings of STK though not unique have characteristic findings. The keratin surface is either parakeratotic or orthokeratotic with spires of chevron parakeratosis imparting a wavy appearance to the keratin surface (Fig. 8c) [32, 35, 36]. The epithelium is acanthotic and cells in the spinous layer may show vacuolated cytoplasm. In most STK, no epithelial dysplasia is identified although the basal layer nuclei may be hyperchromatic. The connective tissue can be uninvolved in STK with little to minimal inflammation. Collagen sclerosis appearing as a band of homogeneous, acellular eosinophilic amyloid-like material has been reported (Fig. 8d). This material is negative for Congo red and positive with periodic acid-Schiff confirming the collagen nature [36]. The collagen sclerosis can be concentrated around nerves, vascular channels and can also result in salivary gland fibrosis.

With discontinuation of smokeless tobacco most lesions resolve within 6 weeks [32, 35, 37]. Larsson, et al. demonstrated both clinical and histologic resolution within 6 months discontinuation of snus use, even in patients with marked furrowing and keratosis [38]. Most epidemiologic studies in North America and Europe show a minor increased risk of oral cancer [33, 39, 40]. However, if lesions

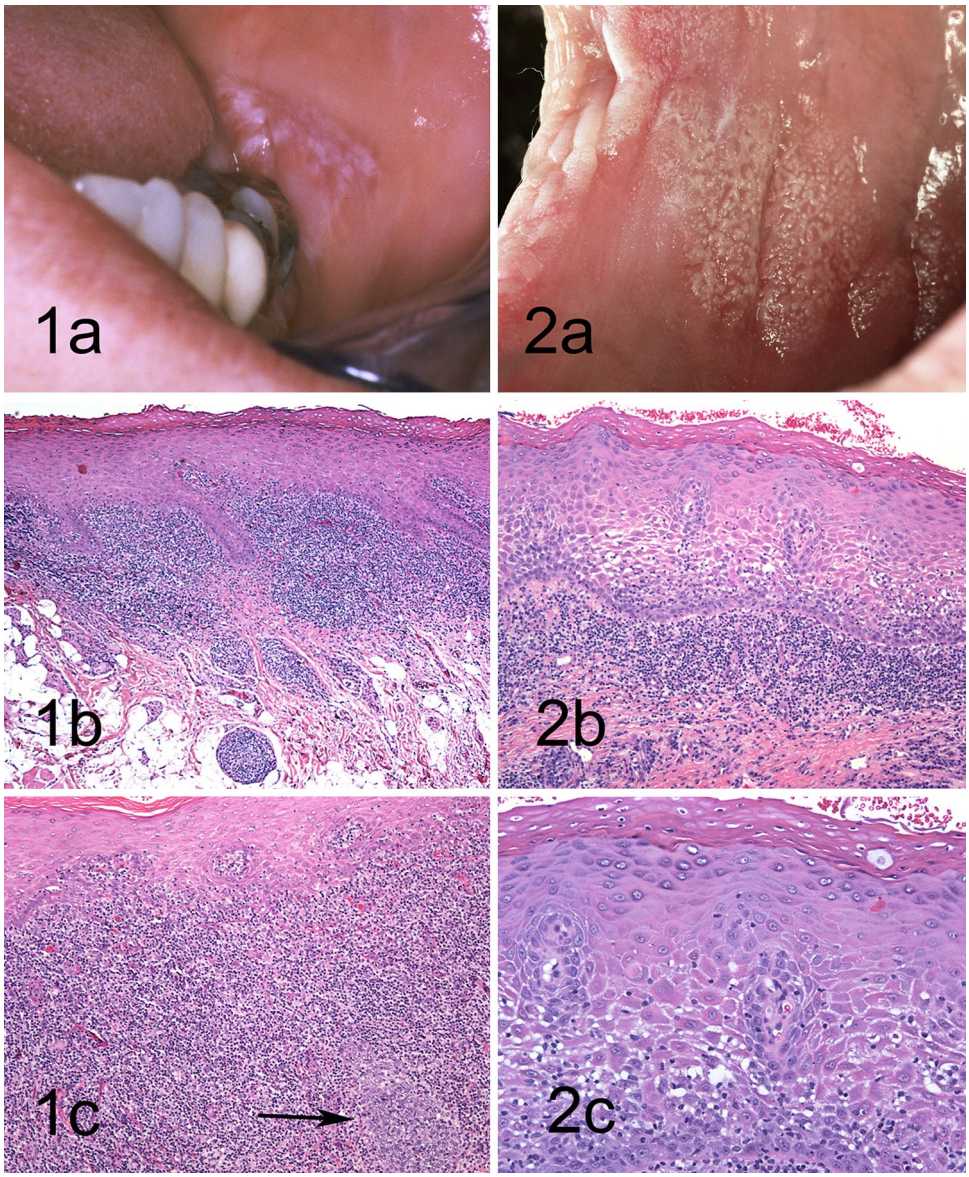

Fig. 7 **1a** Oral lichenoid contact reaction to dental amalgam presenting as areas of erythema and white plaques on the left buccal mucosa. Note the large amalgam restorations that directly contacts the affected mucosa. **1b** Oral lichenoid contact reaction to dental amalgam often has a dense lymphocytic infiltrate subjacent to the epithelial cells. Perivascular inflammation in the deeper lamina propria is present, a feature not typical for oral lichen planus (H&E magnification ×40). **1c** Interface mucositis in amalgam contact reactions are seen and the dense lymphocytic infiltrate can form tertiary follicles (arrow) (H&E magnification ×100). **2a** Oral lichenoid contact reaction of the right buccal mucosa to cinnamon flavored chewing gum. Within 10 days of discontinuing the gum, the lesion completely resolved. **2b** The microscopic features of oral lichenoid contact reaction to cinnamon show marked epithelial acanthosis and intracellular edema. A dense inflammatory cell infiltrate is seen in the superficial lamina propria and generally extends deeper into the lamina propria around vascular spaces (H&E magnification ×100). **2c** Acanthosis, dyskeratotic cells and inflammatory exocytosis is seen along with interface mucositis. The inflammation unlike oral lichen planus is composed of lymphocytes, plasma cells and scattered eosinophils. However, these microscopic findings are relatively non-specific (H&E, magnification ×200)

persist, complete removal is advisable. STK with dysplasia should be treated as oral dysplasia as there is a greater risk for cancer development. Confounding variables including the use of cigarettes and alcohol consumption along with smokeless tobacco use are associated with an increased oral cancer risk [40].

Conclusion

The myriad of clinical findings of reactive white lesions can be challenging when attempting to distinguish from other disorders, including OPMDs. Lesions associated with infections such as oral hairy leukoplakia and

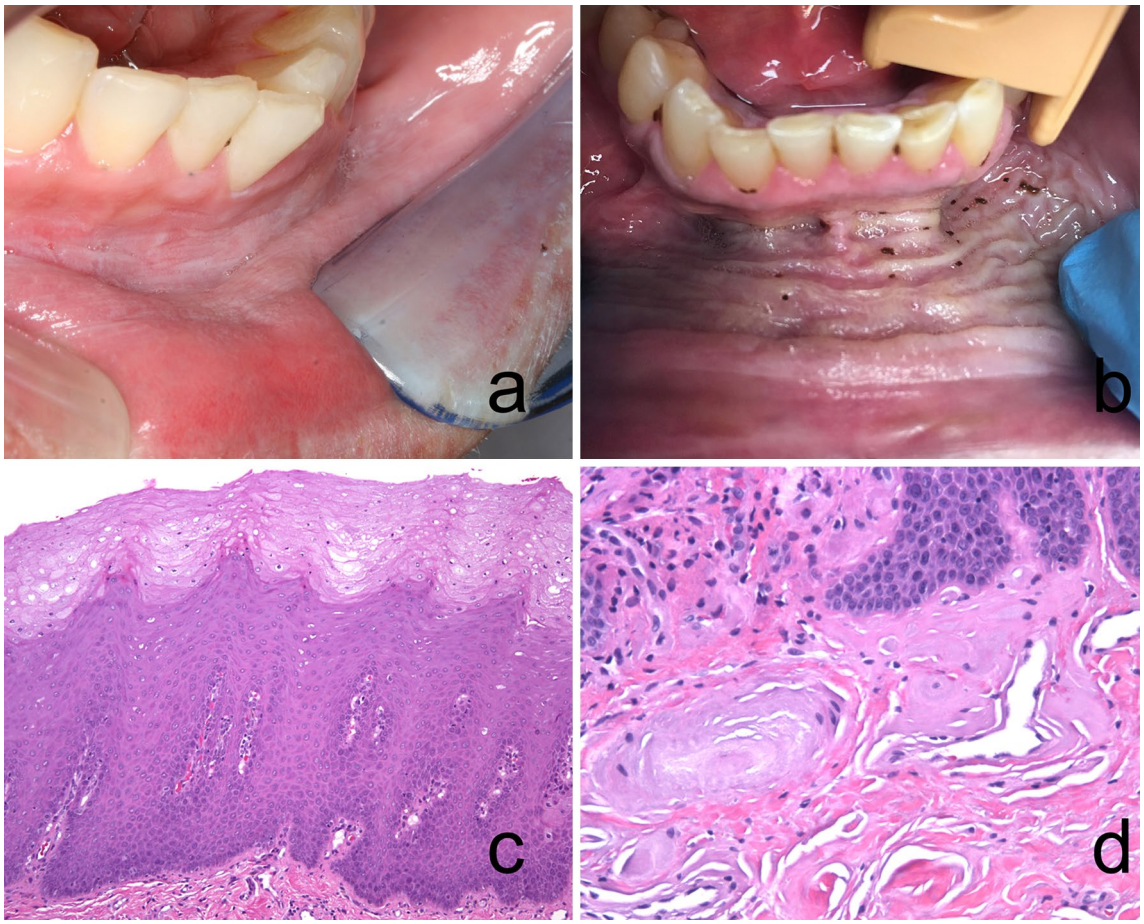

Fig. 8 **a** Typical clinical presentation of an early smokeless tobacco keratosis demonstrating an area of superficial keratosis with slight wrinkling, lacking any appreciative mucosal thickening. **b** A more advanced lesion demonstrates obvious mucosal thickening and wrinkling of the mucosa with intervening furrows. Flecks of smokeless tobacco are present within the lesion. **c** Photomicrograph of smokeless tobacco keratosis shows a corrugated parakeratotic surface and epithelial acanthosis. Prominent chevron keratinization and vacuolated cells in the stratum spinosum are seen. The basal cells show nuclear hyperchromatism but no dysplasia is seen. The connective tissue lacks inflammation. (H&E, magnification ×100). **d** Subepithelial collagen eosinophilia that can be mistaken for amyloid is an unusual finding in smokeless tobacco keratoses. These deposits can be seen around nerves, vessels, salivary glands, and at the epithelial-stroma interface. (H&E, magnification ×100)

hyperplastic candidiasis can have a clinical presentation similar to frictional keratoses. Many reactive white lesions masquerade as oral lichen planus including amalgam reactions and other contact reactions. When there is reasonable doubt about the etiology of a white lesion of the oral mucosa, biopsy should be the gold standard for ruling out "true leukoplakia".

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Compliance with Ethical Standards

Conflict of interest The author declares they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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