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

Non-HPV Papillary Lesions of the Oral Mucosa: Clinical and Histopathologic Features of Reactive and Neoplastic Conditions

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Abstract
Excluding human papillomavirus (HPV)-driven conditions, oral papillary lesions consist of a variety of reactive and neoplastic conditions and, on occasion, can herald internal malignancy or be part of a syndrome. The objectives of this paper are to review the clinical and histopathological features of the most commonly encountered non-HPV papillary conditions of the oral mucosa. These include normal anatomic structures (retrocuspid papillae, lingual tonsils), reactive lesions (hairy tongue, inflammatory papillary hyperplasia), neoplastic lesions (giant cell fibroma), lesions of unknown pathogenesis (verruciform xanthoma, spongiotic gingival hyperplasia) and others associated with syndromes (for instance Cowden syndrome) or representing paraneoplastic conditions (malignant acanthosis nigricans). Common questions regarding differential diagnosis, management, and diagnostic pitfalls are addressed, stressing the importance of clinico-pathologic correlation and collaboration.

Keywords Oral mucosa · Hairy tongue · Giant cell fibroma · Verruciform xanthoma · Malignant acanthosis nigricans · Cowden syndrome

Introduction

The oral cavity is site to various papillary mucosal entities, some of which represent normal anatomy while others are lesional. Papillary oral pathologies are a heterogenous group. Aside from human papillomavirus (HPV)-induced lesions, oral papillary lesions also consist of a variety of reactive and neoplastic conditions and, on occasion, can herald internal malignancy or be a manifestation of a syndromic condition. The objective of this article is to revisit oral conditions that appear papillary, verruciform, hairy or micronodular, while focusing uniquely on reactive and neoplastic lesions that are not associated with HPV. Common questions regarding clinical and histopathologic presentations of these lesions will be addressed. For the pathologist evaluating these lesions, the clinical information should provide key information that compliments the histopathological picture and prevents diagnostic pitfalls. From the clinician's perspective, recognizing the causes and clinical presentations of these conditions will help guide management.

Lymphoid Hyperplasia of the Posterior-Lateral Tongue

The lateral lingual tonsils are aggregates of lymphoid tissue located bilaterally on the posterior-lateral surfaces of the tongue, related to the foliate papillae [1]. Together, the foliate papillae and these lymphoid aggregates can give a pebbly or micronodular appearance to the posterior regions of the lateral surfaces of the tongue [1]. When the lateral lingual tonsils are hypertrophic, they form clustered, nontender papules that may appear yellow or peachy when the lymphoid tissue is close to the surface; or pink-red when the tissue is deeper (Fig. 1) [2]. The cause of lingual tonsil hypertrophy (LTH) is unclear [3]. One research group found that young age, smoking and severe laryngopharyngeal acid reflux were associated with the development of LTH [3].

The diagnosis of LTH can usually be made based on the clinical appearance and history. To the unexperienced examiner, the color and texture change can resemble oral squamous cell carcinoma (OSCC) [4]. However, the bilateral, symmetrical location and soft texture of this tissue should

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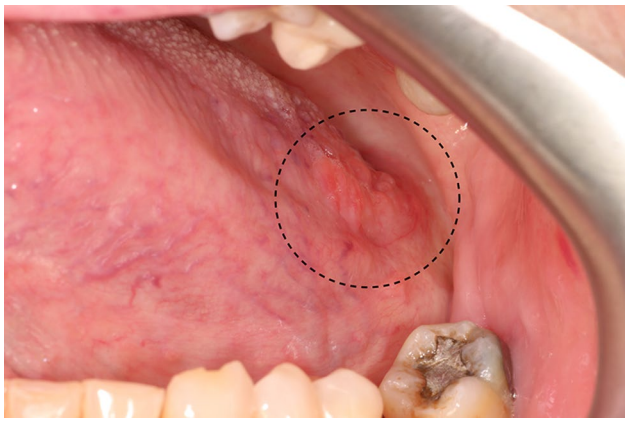

Fig. 1 Lymphoid hyperplasia of the lateral lingual tonsils. The multinodular peach-colored tissue of the posterior lateral tongue (circle) represents hyperplastic lymphoid tissue. The color is due to the presence of lymphocytes below the surface epithelium. The tissue was soft, bilateral and symmetrical

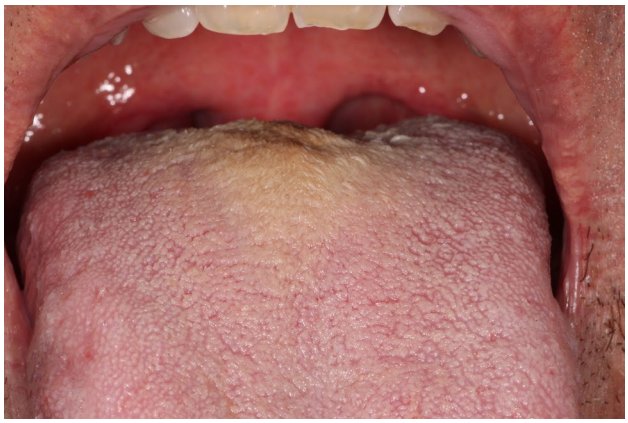

Fig. 2 The hairy appearance of the posterior dorsal surface of the tongue is caused by the elongation of the filiform papillae secondary to keratin buildup

be reassuring [4]. A biopsy can be performed if there is any doubt regarding the clinical diagnosis. Histopathologically, follicular lymphoid hyperplasia is seen. This is considered a benign lymphoproliferative process [4]. Once the diagnosis of follicular lymphoid hyperplasia is confirmed, no treatment is necessary [4].

Hairy Tongue (HT)

As the name suggests, HT is a clinically hairy appearance of the dorsal surface of the tongue. The hair-like projections represent a marked elongation of the filiform papillae due to a buildup of keratin [5]. Keratin buildup can be due to decreased normal keratin desquamation or increased keratin production [6, 7]. The elongated filiform papillae are usually located on the posterior midline of the dorsal tongue. They can extend anteriorly, sparing the tip and lateral borders (Fig. 2) [4]. The filiform papillae can be white, yellow, brown, or even black, due to exogenous pigmentation from food or tobacco, pigment-producing bacteria, or certain medications [6]. Most patients are asymptomatic, however some may complain of halitosis [8], dysgeusia, the unaesthetic appearance of their tongue, or more rarely of nausea and gagging [6, 9].

HT is a usually transient condition associated with poor oral hygiene, a soft diet, anorexia, heavy smoking, oxidizing mouthwashes, xerostomia, antibiotics and xerostomia-inducing medications [7]. The role of *Candida* spp. in the pathogenesis of HT has not been conclusively demonstrated [7]. One must remember that *C. albicans* is part of the normal oral microflora in up to 44% of healthy individuals [10]. Some healthy carriers of *Candida* spp. will also present HT. In these cases, a yeast culture could render false positive results. In addition to this high rate of carriage, the antibiotics or xerostomia-causing drugs associated with development of HT can predispose the patient to developing oral candidiasis, without *Candida* spp. being the cause of HT [11].

Diagnosis of HT is based on the clinical appearance. In instances when a biopsy of the dorsal tongue mucosa is provided, the pathologist must remember that surgical handling of the specimen may have given it a polypoid appearance, for instance if the base of the specimen was pinched with forceps. This altered architecture of the filiform papillae-bearing mucosa could lead to the erroneous diagnosis of squamous papilloma. Attention should be taken not to confuse HT with *oral hairy leukoplakia*. Clinically and microscopically, both conditions appear quite different [12]. Only their names sound alike.

Treatment of HT consists of gentle debridement by regular tongue brushing complimented by tongue scraping [8], patient reassurance regarding the benign and transient nature of the condition [7] and modification of chronic predisposing factors [6]. The return to a solid food diet will also improve the appearance of the tongue for some patients.

Inflammatory Papillary Hyperplasia (IPH)

IPH is a reactive tissue overgrowth that typically develops on the denture-bearing hard palate [13, 14]. Factors implicated in the etiopathology include candidiasis, poor oral hygiene, an ill-fitting or old denture, smoking, old age, continuous and nighttime wear of a denture [14–16]. IPH has been considered part of the spectrum of denture stomatitis (Newton's classification type III) [17]. Clinically, the hard palate mucosa appears hyperemic and covered in small, painless,

nodular or papillary growths. These changes usually begin on the palatal vault but can extend to involve the entire hard palate [4]. The degree of inflammation is variable (Fig. 3a) [13]. IPF can also be seen in dentate patients with a deep palatal vault or who breathe with their mouths [4, 16]. IPH is usually asymptomatic and most patients are unaware of its presence [13].

The diagnosis of IPH is based on the clinical appearance of the mucosa. A biopsy is rarely indicated. When tissue is submitted, papillary projections are seen, surfaced by non-keratotic or parakeratotic stratified squamous epithelium [18]. The epithelium alternates between areas of atrophy and acanthosis extending deep within the lamina propria [18]. Pseudoepitheliomatous hyperplasia can be present, which should not be mistaken for a well-differentiated OSCC [4, 19]. The lamina propria can be edematous or fibrotic, and supports a lymphoplasmacytic infiltrate (Fig. 3b) [4]. Candidal hyphae are seldom identified, since they are mostly located on the tissue-bearing surface of the denture [19].

Management of IPH consists of providing patient education regarding denture wear and hygiene, improving denture fit, fabricating new dentures, and treating fungal infection [17]. Once the sources of inflammation have been removed, the erythema and edema resolve, but the papillary appearance of the mucosa may not completely disappear [16]. In cases where persisting fibrous tissue obstructs the proper fitting of a maxillary denture, the excess tissue can be surgically removed [18]. In most situations, however, IPH requires no further treatment once the inflammation has reduced [13].

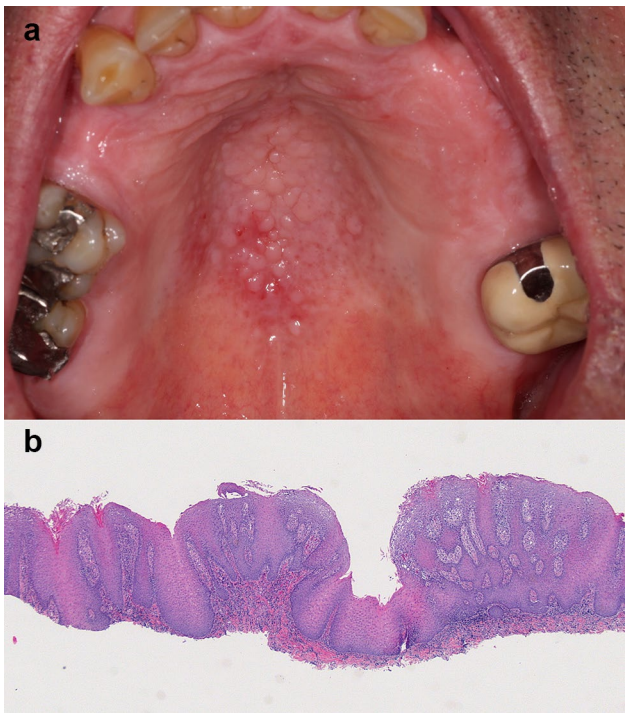

Fig. 3 **a** The palatal vault is covered by small fibrous papules representing inflammatory papillary hyperplasia. **b** Low-power view showing fibrous and epithelial hyperplasia resulting in papillary surface projections. A chronic inflammatory infiltrate is present in the superficial connective tissue and extends into the epithelium. Periodic acid Schiff staining revealed the presence of fungal hyphae in the keratin layer, compatible with *Candida* spp. (original magnification ×25, Hematoxylin & eosin)

Giant Cell Fibroma (GCF)

GCF is a benign fibrous tumor with distinct clinical and pathological features [20]. Unlike a traumatic fibroma, it is not induced by chronic low-grade trauma. GCF represents approximately 4.7% of all oral benign fibrous growths submitted for biopsy [20]. The lesion predominantly affects Caucasians, has a slight female predilection, and a peak incidence in the second decade of life. In a study of 434 cases, 60% occurred before the age of 30 [20].

GCF presents as a small, asymptomatic, pale pink, pedunculated or sessile fibrous nodule. Most lesions measure less than 1 cm in diameter and have limited growth potential - the average size being 4 mm [20]. The gingiva, tongue, palate, buccal mucosa and lip are the sites of predilection [20]. The lesion can be present for years before being noticed by the patient. The surface of the lesion can be smooth and dome-shaped, finely bosselated or papillary (Fig. 4a). Smooth lesions will inspire a clinical differential diagnosis including traumatic fibroma, peripheral ossifying fibroma, pyogenic granuloma, and peripheral giant cell granuloma [20]. Papillary lesions often lead to a clinical diagnosis of squamous papilloma or verruca vulgaris [20].

Histopathologically, GCF presents as a nodular mass with a smooth or pebbly surface [20]. The body of the nodule is composed of fibro-vascular connective tissue surfaced by a thin keratotic stratified squamous epithelium [20]. The rete ridges are often elongated and narrow (Fig. 4b). The distinguishing characteristic is the presence of multiple plump, stellate, bi- or multinucleated fibroblasts in the superficial connective tissue (Fig. 4c) [20, 21]. Melanin incontinence and melanophages are occasionally present below the basement membrane [22]. Other lesions involving the skin and mucous membranes have a similar microscopic appearance. These include the fibrous papule of the nose, ungual fibroma, acral fibrokeratoma and fibroblastoma [20]. Mucosal lesions include the retrocuspid papillae (RCP) (discussed below) and pearly penile papules [20].

A conservative excision is usually curative. Recurrences have been documented but are rare [20].

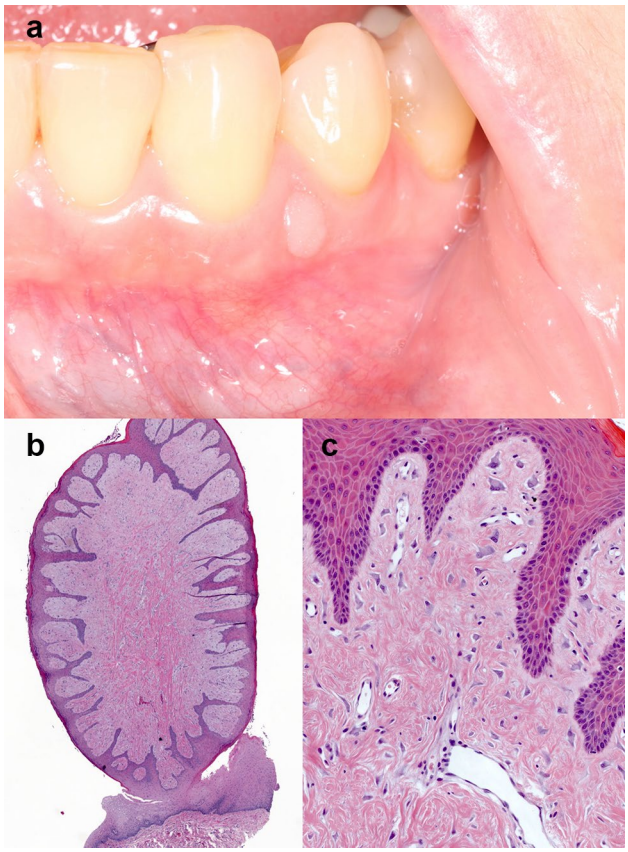

Fig. 4 **a** GCF of the mandibular facial gingiva presenting as a pale pink sessile nodule with a pebbly surface. **b** Low-power view of a GCF. The pedunculated, bosselated, polypoid nodule is composed of fibrous connective tissue and orthokeratotic stratified squamous epithelium. Note: the elongated, pointed rete ridges (original magnification ×25, Hematoxylin & eosin). **c** High-power view of the papillary chorion in a GCF. Note: the presence of multiple plump, stellate-shaped multinuclated fibroblasts (original magnification ×200, Hematoxylin & eosin)

Retrocuspid Papillae (RCP)

RCP are small, sessile, pink papules, with or without a papillary surface, located on the gingiva lingual to the mandibular cuspids [23]. RCP are asymptomatic, often bilateral and measure < 5 mm in diameter (Fig. 5). They have been reported in 11%–99% of children and young adults under 20 years of age [23]. This prevalence decreases to approximately 8% by the 5th decade of life, which supports the idea that RCP represent a normal anatomic structure that regresses with age [23]. Once recognized, no treatment is indicated [24].

The clinical significance of RCPs is that they may mimic gingival growths, from which they must be distinguished to avoid unnecessary biopsy [23, 24]. Since they are microscopically similar to GCF, the proper diagnosis requires clinico-pathologic correlation.

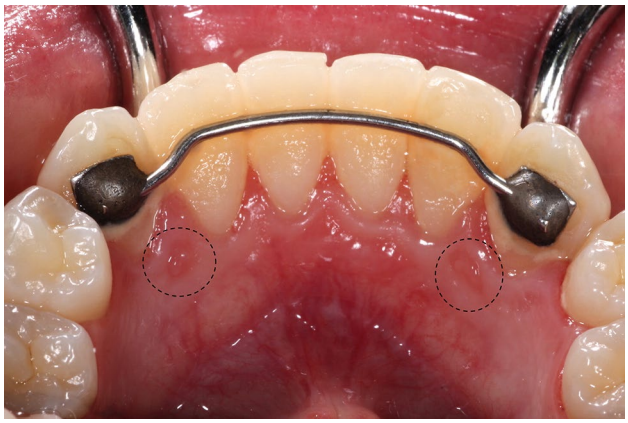

Fig. 5 RCP presenting as bilateral sessile papules on the gingiva lingual to the mandibular canines (circles)

Spongiotic Gingival Hyperplasia (SGH)

SGH is a distinctive subtype of gingival hyperplasia with characteristic clinical and histological features. The first cases were published in 2007 and 2008 under the names *juvenile spongiotic gingivitis* [25] and *localized juvenile* SGH [26], respectively. Recent cases have been reported in adults and with a multifocal distribution, which argues against the designations "localized" and "juvenile" [27]. The exact cause remains unknown [27]. SGH does not seem to be related to trauma, hormonal changes of puberty, accumulation of dental plaque or calculus, or foreign body integration [25–27]. Immunohistochemical studies have shown that SGH could represent exteriorized or ectopic junctional epithelium of the gingiva that has become hyperplastic in response to inflammation, thus implying a developmental etiology [25, 28].

The classic presentation is a bright red, slightly papillary/granular/velvety, well-demarcated, painless but easily-bleeding gingival overgrowth located on the facial gingiva of the anterior teeth (Fig. 6a) [25, 26]. The maxillary gingiva is affected five times more frequently than the mandible [25]. SGH can involve the marginal gingiva, attached gingiva and the interdental papillae [25, 26]. The majority of lesions are single, localized and measure less than 1 cm in diameter [25–27, 29]. They can be present several months to a few years before diagnosis [25, 27, 29]. A slight female predilection is often reported [25, 26, 29]. The mean age at presentation is approximately 12 years, but SGH can be identified anytime from childhood to adulthood [25, 26, 29]. Up to 82% of reported cases are in Caucasians [26, 29].

Microscopically, well-formed SGH presents as a papillary nodule surfaced by non-keratinized, variably acanthotic, spongiotic stratified squamous epithelium with elongated rete ridges [25, 26]. Neutrophilic exocytosis within the epithelium is prominent [26]. The papillary

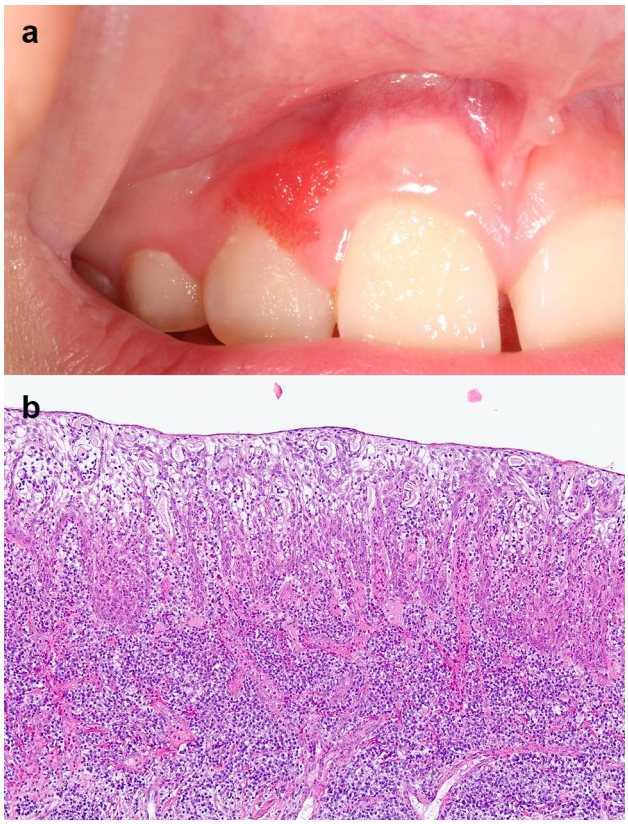

Fig. 6 **a** SGH presenting as a localized bright red papillary growth of the facial maxillary gingiva in a 9-year-old female. **b** Medium-power view of SGH in a 33-year-old male. This lesion of recent onset lacks a papillary architecture, but shows epithelial hyperplasia, spongiosis, an absent keratin layer, neutrophilic exocytosis, and a dense chronic inflammatory infiltrate in the connective tissue (original magnification ×100, Hematoxylin & eosin)

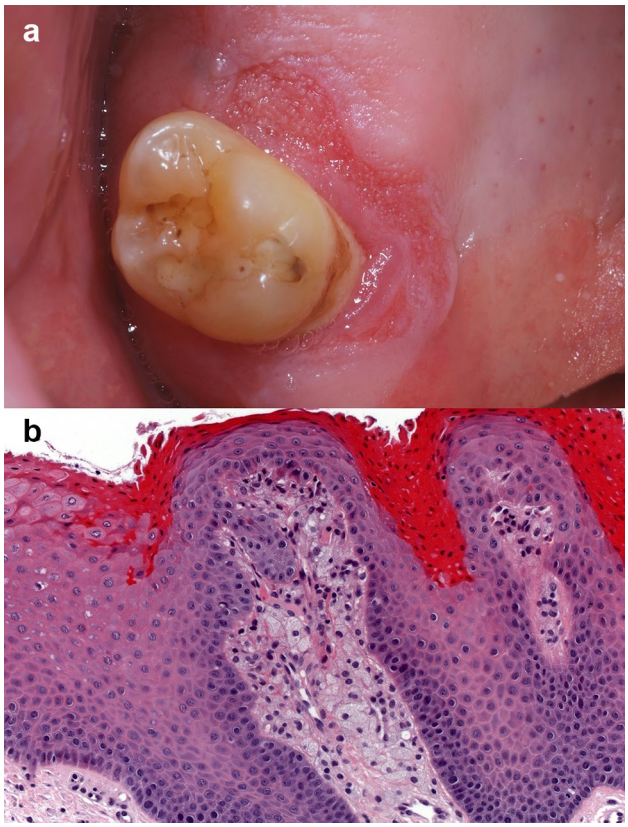

Fig. 7 **a** VX presenting as a red plaque with a granular surface on the gingiva mesio-palatal to a maxillary molar. (Courtesy of Dr. Benoît Lalonde). **b** High-power view of a VX demonstrating the collections of foamy macrophages in the connective tissue papillae, papillomatosis and orange hyperparakeratosis (original magnification ×200, Hematoxylin & eosin) (Courtesy of Dr. Adel Kauzman)

projections are supported by loose fibro-vascular connective tissue with atrophic overlying epithelium. The connective tissue papillae show vasodilation, congestion and support a chronic inflammatory infiltrate consisting mostly of lymphocytes, plasma cells and neutrophils [26]. In the initial stages, lesions appear flat and less hyperplastic, but many of the other characteristic histologic features are present (Fig. 6b) [25]. HPV is not implicated in the development of this lesion [29]. All cell layers of the lesional epithelium tend to be cytokeratin (CK) 19 and CK 8/18 positive [27, 28].

The appropriate treatment for SGH remains unknown. Since most published cases were excised, little is known on the natural history of the lesion. Recurrence rates between 6% and 28% have been reported for solitary lesions [25, 26, 29], and 38.5% for multifocal lesions [27]. Spontaneous regression after a period of 15 months has been well documented [27]. This could explain the rare occurrence in adults when compared to the significant predilection in children.

Verruciform Xanthoma (VX)

VX is an uncommon benign mucocutaneous lesion of unknown etiology [30], characterized by the presence of numerous lipid-laden histiocytes below the epithelium [31]. The oral cavity is the site of predilection, but genital lesions have also been reported [32]. Case series with more than ten patients have shown a slight male predilection and an average age at diagnosis between 45 and 53 years [30]. Several etiologic factors have been proposed, including trauma, inflammation, an altered immunological response, epithelial degeneration and lipid accumulation [30]. Contrary to other dermal xanthomas (such as xanthelasma palpebrarum) that can signalize dyslipidemia, atherothrombotic disease or type II diabetes [33], there is no such association with VX. Interestingly, VX is part of CHILD syndrome, a trait caused by mutations in the *NSDHL* gene involved in the cholesterol biosynthetic pathway [34]. Although VX is a papillary lesion, HPV

Table 1 Syndromes and skin disorders associated with oral papillomatosis

Name(s)	Gene mutation	Prevalence	Reported oral anomalies	Other associated manifestations	Selected references
Multiple hamartoma syndrome (*PTEN* hamartoma tumor syndrome, Cowden syndrome)	*PTEN* gene	1 in 2,50,000	Multiple gingival and mucosal papillary papules	Facial trichilemmomas, acral (palmoplantar) keratosis. Cutaneous hemangiomas, xanthomas, lipomas and neuromas. Colorectal, mammary, thyroidal and genitourinary cancers	[36]
Linear epidermal nevus	*FGFR3* and *PIC3CA* genes (in 40% of cases) [49]	1 in 1000	Unilateral/midline papules/nodules with a papillary/verrucous surface. Lesions do not cross the midline and have been found on the lips, tongue, buccal mucosa, hard and soft palate and gingiva. One or more hypoplastic or congenitally missing teeth	Tan or brown verrucous papules (keratinocytic epidermal nevi), arranged linearly following Blaschko's lines. Present at birth or during childhood, grows slowly until adolescence Localized lesions (nevus unius lateris) = confined to one side of body Diffuse (ichthiosis hystrix) = extensive bilateral lesions	[39, 40]
Sebaceous nevus syndrome (Schimmelpenning-Feuerstein-Mims syndrome)	*HRAS* gene [49]	Unknown	Unilateral, focal or linear papillomatous growths of the lips, tongue, gingiva, palate or buccal mucosa, extending from the adjacent skin. Anodontia and hypoplastic teeth	Sebaceous nevus following Blaschko's lines of the head and neck, mental retardation, seizures, hemiparesis, eyelid colobomas	[41–43]
Focal dermal hypoplasia (Goltz syndrome)	*PORCN* gene	Unknown	Intraoral papilloma or papillary gingival hyperplasia. Intraoral lipoma. Vertical enamel grooving, peg shaped teeth, enamel hypoplasia. Cleft lip and cleft palate	Thinning of the skin, herniation of adipose tissue, hyperpigmentation, hypopigmentation following Blaschko's lines, abnormalities of the eyes, nervous, cardiovascular, gastrointestinal, reproductive and musculoskeletal systems	[44, 45]
Ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome	*p63* gene	Unknown	Cleft lip/cleft palate, perioral papillomatosis involving lips, commissures, and occasionally the buccal mucosa, hypodontia, microdontia, enamel hypoplasia	Ectrodactyly, syndactyly, ectodermal dysplasia, tear duct anomalies, genitourinary anomalies, deafness	[46, 47]
Costello syndrome	*HRAS* gene	From 1 in 3,00,000 to 1 in 1.25 million [50]	Verrucous lesions arranged in plaques around the mouth and nares	Delayed development and delayed mental progression, distinctive facial features, short stature, redundant skin of neck, palms, soles, fingers, hyperflexible joints and curly hair	[48]
Acanthosis nigricans (AN)	Acquired condition	Varies with underlying cause and geographical region	Diffuse, finely papillary lesional areas most often involving the lips, labial commissures, palate, buccal mucosa, and tongue. Minimal or no melanin pigmentation	Finely papillary, keratotic, brown, asymptomatic patches affecting the flexural surfaces of the skin Malignant AN: associated with gastrointestinal or genito-urinary carcinoma Benign AN: associated with obesity, diabetes, endocrinopathies, medications	[37, 38]

has only been detected in a few instances and no definitive viral cause has been recognized [35].

VX appears as a well-demarcated, painless, slow-growing, plaque or nodule with a verrucous or granular surface [32]. The color can range from yellow, pink, white or red (Fig. 7) [30, 32]. The size of the lesion rarely exceeds 2 cm in diameter [30, 32]. The majority of cases occur on the masticatory mucosa (attached gingiva and hard palate). Other oral mucosal sites are less commonly affected [30]. Clinically, VX is often mistaken for a squamous papilloma, verruca vulgaris, condyloma, leukoplakia and occasionally for early verrucous carcinoma or OSCC [30, 32]. Most lesions are excised and diagnosed microscopically.

The histological features of VX are similar for all lesions [32]. They include a papillary proliferation of stratified squamous epithelium associated with hyperparakeratosis. The thick parakeratin layer tends to have a noticeable salmon or orange color when stained with hematoxylin and eosin [30] and extends into the epithelial crypts to form parakeratin plugs [30, 31]. The rete ridges are uniformly elongated [31]. The outstanding characteristic feature of VX is the presence of numerous foamy lipid-laden histiocytes (xanthoma-like cells) within the connective tissue papillae. These foamy cells do not extend below the tips of the rete ridges [31]. They show cytoplasmic immunopositivity for CD69, CD63 and CD163 [30]. A moderate chronic inflammatory infiltrate is dispersed in the underlying connective tissue [30].

VX is treated by conservative surgical excision. The prognosis is excellent [30]. There are no reports of VX undergoing malignant transformation.

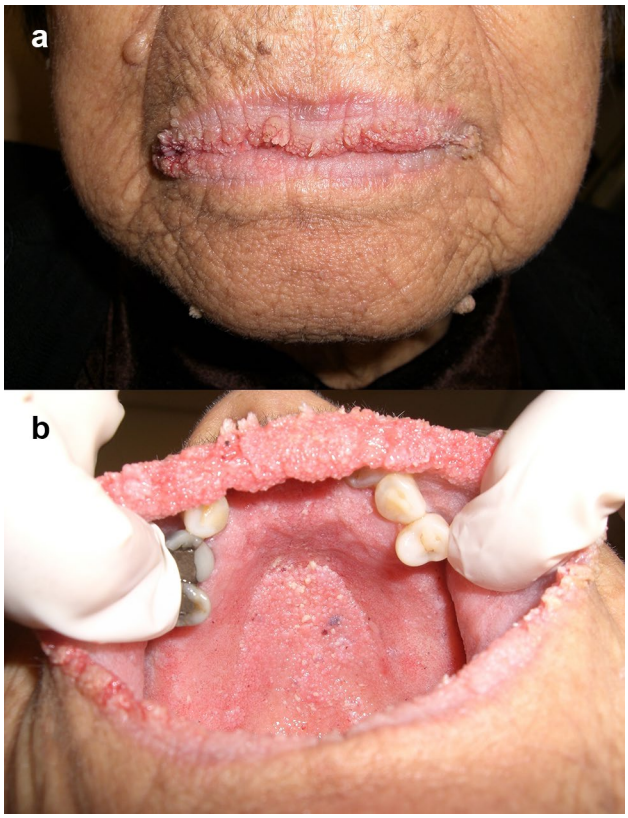

Fig. 8 **a** Malignant acanthosis nigricans affecting the vermilion and commissures of the lips. A gastric carcinoma was discovered following the development of florid cutaneous and mucosal papillomatosis (Courtesy of Dr. Hagen B. E. Klieb). **b** Same patient as **a**. Note: the florid papillomatous lesions on the hard palate, alveolar ridge and upper labial mucosa. This patient's case history was published in reference [38] (Courtesy of Dr. Hagen B. E. Klieb)

Syndromes and Skin Disorders Presenting with Oral Papillary Lesions

Oral papillomatosis is part of a variety of skin disorders and syndromes (Table 1). The development of multiple sessile papillomatous, white–pink, coalescent papules on the keratinized and non-keratinized oral mucosa can be an early clue toward diagnosis of multiple hamartoma syndrome [36]. The sudden onset of florid papillomatosis of the lips, labial commissures or oral mucosa is characteristic of acanthosis nigricans, a paraneoplastic condition associated with gastrointestinal malignancy (Fig. 8a, b) [37, 38]. Oral papillary lesions arranged linearly, distributed unilaterally or along the midline (following Blaschko's lines) are a feature of linear epidermal nevus [39, 40], sebaceous nevus syndrome [41–43] and focal dermal hypoplasia [44, 45]. Perioral papillomatosis has been reported in patients with ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome [46, 47] and Costello syndrome [48]. For a complete discussion of the reported oral anomalies and other manifestations that characterize each syndrome, please refer to the references included in Table 1.

Conclusion

Oral mucosal lesions with a papillary architecture readily bring to mind HPV-related conditions. However, papillary lesions also include a variety of developmental, reactive and neoplastic conditions not driven by HPV infection. In this review, attention was placed on prevalent lesions that could be encountered in everyday clinical or laboratory practice of oral pathology. Clinicians are reminded that oral papillomatosis is a component of a variety of syndromes and, on occasion, can be a paraneoplastic condition. Rare conditions (for example oral condylomata lata of secondary syphilis [51], sialadenoma papilliferum and inverted ductal papilloma) were not discussed, but may be considered in the appropriate clinical setting. In addition, dysplastic and malignant oral

verrucous or papillary lesions, notably proliferative verrucous leukoplakia, verrucous carcinoma and papillary OSCC, were excluded since a lack of consensus exists on the role of HPV in these lesions [52]. As in many situations in medical care, clinico-pathologic correlation and collaboration is often essential to achieving the proper diagnosis. Clinicians and pathologists profit from each other's complimentary knowledge, ultimately to the patient's benefit.

Compliance with Ethical Standards

Conflict of interest Gisele N. Mainville declares that she has no conflict of interest.

Informed Consent Informed consent was obtained from all individuals.

Research Involving Human and Animal Participants This article does not contain any studies with human participants or animals performed by any of the authors.

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