Head and Neck Pathology (2019) 13:80–90
https://doi.org/10.1007/s12105-019-01003-7

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

HPV-Related Papillary Lesions of the Oral Mucosa: A Review

Sasha J. Betz[1]

Received: 24 October 2018 / Accepted: 2 January 2019 / Published online: 29 January 2019

Abstract
Human papillomaviruses (HPVs) are causative of a group of clinically papillary lesions. The HPV-related lesions of the oral cavity include squamous papilloma, condyloma acuminatum, verruca vulgaris, and multifocal epithelial hyperplasia. Benign entities, such as verruciform xanthoma or giant cell fibroma, as well as malignancies, such as papillary squamous cell carcinoma and verrucous carcinoma, may be considered in the clinical and/or histologic differential diagnoses of these lesions. Mechanisms of infection, epidemiology, clinical presentations, histologic features, and differential diagnoses of the HPV-related oral pathologies are discussed. Current concepts of viral transmission, especially as pertaining to lesions in pediatric patients, and the impacts of HPV vaccination are reviewed.

Keywords Human papillomavirus · Squamous papilloma · Oral warts · Multifocal epithelial hyperplasia · Squamous cell carcinoma · HPV transmission

Human Papillomavirus and the Biology of Infection

There are over two hundred human papillomaviruses (HPVs) as categorized by genotype [1]. The HPVs are sub-grouped according to differences in their DNA sequences [1]. The largest subgroup is the α group, with HPV genotypes that primarily infect mucosal epithelia, followed by the β group, which preferentially infect cutaneous epithelia [1]. The tropism for certain tissues is likely due to variations in viral gene function and expression, but not yet fully elucidated [2, 3]. Both α and β groups contain HPV types that are causative of oral lesions, including squamous papilloma (α group) and verruca vulgaris (β group) [1]. In a recent systematic review and meta-analysis, it was determined that approximately 7.7% of healthy subjects harbor HPV in the oral region [4].

The viruses may be spread vertically, from mother to offspring, or horizontally between individuals [5]. Although HPV is considered the most common sexually transmitted infection, the virus may also be transmitted non-sexually through skin-to-skin, skin-to-mucosa, or mucosa-to-mucosa routes [5]. Oral HPV has been detected in exfoliated cells of newborns delivered vaginally and via caesarean births, indicating transmission through the placenta or amniotic fluid may occur in addition to birth canal exposure [6]. Other proposed mechanisms for oral infection, particularly in children, include autoinoculation from cutaneous lesions, fomites, breast feeding, or bathing [6]. In adults or in instances of child abuse, oral sex and open-mouthed kissing are significantly associated with oral HPV infections, with the odds of infection increasing with the number of lifetime oral and vaginal sexual partners [7].

In establishing a productive lifecycle, HPV infects basilar epithelial stem cells [2]. Access is facilitated through microabrasion or trauma, or in the properties of specialized epithelia such as that of the tonsils, bulge region of the hair follicle, or squamo-columnar junction of the cervix [1, 2]. After gaining entry into the cell via endocytosis, the episomal genome enters the nucleus where viral transcription is initiated [1]. Viral replication is completed in parallel with that of the basilar cell, and viral genomes tethered to host chromosomes are then propagated to new daughter cells [1]. As infected cells differentiate from basilar cells to keratinocytes, the viral genome copies are amplified and particles are assembled [1]. By the time keratinocytes desquamate from the upper epithelial layers, the cells are teeming with thousands of viruses, ready to infect the next host [8].

✉ Sasha J. Betz
sasha.j.betz.mil@mail.mil

[1] Division of Anatomic Pathology, Naval Medical Center San Diego, 34800 Bob Wilson Drive, San Diego, CA 92134-5000, USA

The success of HPV lies, in part, in evasion of host immune surveillance [9]. Some of the inherent properties of their target cell, the keratinocyte, assist in this feat. Firstly, keratinocytes are peripheral cells [10]. The viruses enter the cells from the environment with minimal exposure to effector cells of the innate immune system, as the infection is entirely intraepithelial [10, 11]. The propagation of the virus through replication of the infected stem cells to their daughter cells, while maintaining low genome copy numbers and without secreted proteins, further allows the virus to escape immune detection [3]. As the keratinocytes are fated for death and desquamation, no immune response is triggered through cytopathic cell death or viremia [9–11]. Thus accessibility, intimate relationship with the keratinocyte life cycle, and lack of immune response to viremia or apoptosis partially explain the success of HPV in immune evasion [2]. Other viral defense strategies impede the immune system directly. These mechanisms include modulation of interferons, antigen processing, and T cells, and differ according to HPV protein functions of the varying subtypes [2, 11]. The finding of low antibody titers after HPV infection, too low to have protective effects, demonstrates the efficacy of these mechanisms [10].

Some of the key differences of HPV proteins, especially E6 and E7, attribute to subtype stratification into low-risk groups (LR-HPVs), associated with benign lesions of the skin and mucosa, and high-risk groups (HR-HPVs), subtypes causative of malignancy [3]. Briefly, the HR-HPV E6 protein is oncogenic in several functions including binding and degrading tumor suppressor protein p53 as well as inhibiting apoptosis, keratinocyte differentiation, and interferon responses [3]. HR-HPV E7 stimulates cell-cycle entry and progression, binds and degrades tumor suppressor pRb, and introduces genome instability [3]. The LR-HPV E6 and E7 proteins share some of the same functions, but the binding of p53 and pRb, respectively, is weaker and does not lead to degradation [3]. The E6 inhibition of the interferon response is weaker, and E7 does not cause genome instability [3]. Further discussion of the molecular mechanisms of HPV is beyond the scope of this review; however, it is important for both the clinician and patient to conceptualize that innate differences in the HR- and LR-HPVs account for risk, or lack thereof, for malignancy. Simply speaking, an oral squamous papilloma is not transformative to HPV-related squamous cell carcinoma because the causative virus, a LR-HPV, lacks oncogenic properties [3].

Unlike the oropharynx, where over 70% of squamous cell carcinomas are HR-HPV related, the etiologic fraction of HR-HPV associated oral cavity squamous cell carcinomas (OCSCC) is less than 6% [12]. The survival outcomes for this small group are not defined, and routine HPV testing is not currently recommended for OCSCC [12].

The majority of oral HPV infections are subclinical and cleared within 1 to 2 years (median 6 months) [1, 11]. While the literature and methodologies vary, studies show a minority of individuals, in the 0–23.1% range, experience persistent infection [4]. The incidence of lesion formation in the oral cavity is approximately 3% [13]. As additional study is necessary to better define any differences in the clinical and histopathologic presentations of HPV-associated and non-associated OCSCC, this review will focus solely on the benign HPV-related papillary lesions of the oral cavity.

Human Papillomavirus-Related Lesions of the Oral Cavity

The benign HPV-related lesions of the oral cavity comprise verruca vulgaris (common wart) (VV), squamous papilloma (SP), condyloma acuminatum (CA), and multifocal epithelial hyperplasia (MEH) (Table 1). These lesions share clinical and histologic features amongst themselves as well as with other lesions of inflammatory, syndrome-associated, or malignant etiologies [14]. Consideration of the clinical and histologic characteristics of each entity, as well as its potential mimickers, is useful to the clinician and pathologist when managing these lesions.

Of note, some literature argues for the combination of SP and CA due to HPV 6 and 11 causality of both lesions, as well as overlap of histologic and clinical presentations [15]. In this review, these lesions are considered separately as is convention in the head and neck. It is acknowledged that the distinguishing criteria may be ambiguous and subject to change with future revelations regarding the pathophysiology of these entities.

Table 1 Benign HPV-mediated lesions of the oral cavity, types associated, and sites most commonly affected

Lesion	Commonly associated HPV types	Commonly affected intraoral sites
Common wart (verruca vulgaris)	2, 4	Vermillion border, labial mucosa, anterior tongue
Squamous papilloma	6, 11	Palate, tongue, labial mucosa
Multifocal epithelial hyperplasia	13, 32	Buccal and labial mucosa, tongue
Condyloma acuminatum	6, 11, 16, 18	Labial mucosa, soft palate, lingual frenum

Verruca Vulgaris

VV, or the common wart, is the main presentation of cutaneous HPV infection and accounts for 70% of warts [16, 17]. An estimated 10% of children and young adults are affected, with peak incidence occurring in teenagers ages 12–16 [16]. VV may be found anywhere on the skin, but is most common on the periungal region of the hands [18]. While common on the skin, VV is relatively uncommon intraorally [18, 19]. Autoinoculation is a main mode of transmission and may occur when a child bites the lesions of their fingers or sucks their thumb [18, 19].

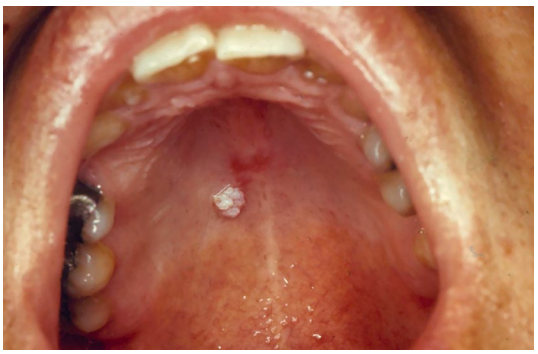

Fig. 1 Clinical image of a verruca vulgaris of the palate. Note the sessile base and verrucous surface. *Photograph courtesy of Dr. Duane Schafer*

Clinically, the mucosal lesions appear similarly to their cutaneous counterparts [18, 19]. The labial mucosa and palate are the most common intraoral sites [19]. The lesions are pink to white, sessile, usually less than one centimeter, and display exophytic fronds (Fig. 1; Table 2) [20]. Seldom, a few VV may occur simultaneously or in clusters, representing multiple sites of infection, but solitary lesions are typical [20].

The histologic presentation is identical to that of cutaneous VV (Fig. 2; Table 2) [18]. Exophytic projections with a verrucous architecture are apparent at low power, with inwards cupping of the rete ridges (Fig. 2a) [18]. Fibrovascular cores are surfaced by acanthotic epithelium demonstrating a prominent granular cell layer. Thick keratinization imparts a chevron or "church spire" appearance (Fig. 2a, b) [18]. Koilocytes, cells demonstrating the viral cytopathic effect of HPV, are characterized by a shrunken, "raisin-like", eccentrically placed nucleus with a vacuolated cytoplasm halo (Fig. 2c) [18]. These cells are often identified in the upper epithelial layers, proximal to or within the granular cell layer [18]. Basilar and parabasilar mitotic figures may be present and slightly increased, but atypical forms are not identified (Fig. 2c) [18].

The clinical and histologic differential diagnosis includes papillary lesions of various etiologies, including benign and

Table 2 Clinical and histologic features of the benign HPV-related lesions of the oral cavity

Entity	Clinical features	Histologic features
Verruca vulgaris	Less than 1 cm	Exophytic fronds with fibrovascular cores
	White or pink	Inward cupping of rete ridges
	Discrete/well-defined	Prominent keratin spires
	Verrucous surface	Prominent granular cell layer
	Sessile	Koilocytes
	Usually solitary	Basilar and parabasilar mitotic figures without atypia
Squamous papilloma	Less than 1 cm	Exophytic fronds with fibrovascular cores
	White to pink/red	Varying keratinization
	"Finger-like" fronds or "cauliflower" surface texture	Koilocytes
	Pedunculated	Basilar and parabasilar mitotic figures without atypia
Condyloma acuminatum	Exophytic fronds with fibrovascular cores	Exophytic projections with fibrovascular cores
	Varying keratinization	Bulbous rete pegs
	Koilocytes	Deep crypts lined by parakeratin
	Basilar and parabasilar mitotic figures without atypia	Koilocytes
	Exophytic fronds with fibrovascular cores	Basilar and parabasilar mitotic figures without atypia
Multifocal epithelial hyperplasia	Generalized presentation	Exophytic with nodular or papillomatous surface architecture
	Multiple lesions that may coalesce	Acanthotic, anastomosing rete ridges
	White to pink	Mitosoid bodies
	Papulonodular or papillomatous presentations	Koilocytes
	Usually sessile	Basilar and parabasilar mitotic figures without atypia

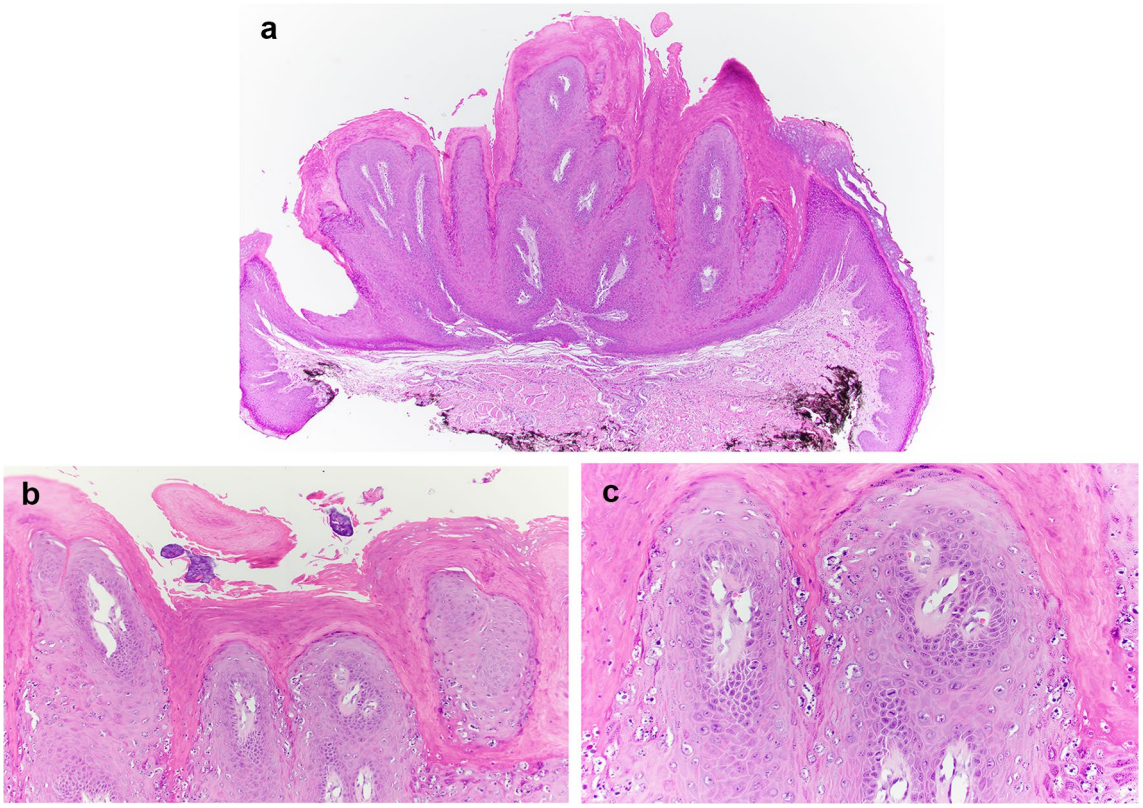

Fig. 2 Histologic features of verruca vulgaris. **a** Low power view. Inwards cupping of the rete ridges and exophytic fronds with thick keratin spires are apparent. A prominent granular cell layer is present. **b** Medium power demonstrates thick keratin and associated bacterial aggregates. **c** Koilocytes and scattered mitotic figures are visible at high power

malignant entities. Verruciform xanthoma (VX), SP, and CA are among the benign mimickers [21]. VX and SP appear similarly to VV, and are best distinguished by histology [21]. VXs are sessile lesions that sometimes impart a yellow hue and are more likely to occur on the gingiva [21]. Histologically, they are differentiated by the presence of foamy, lipid-laden histiocytes within fibrovascular cores [21]. These "xanthoma cells," in combination with orange parakeratin plugging of crypts, are characteristic [21]. Meanwhile, SPs display less prominent keratinization and granular cell layers [14]. They tend to be pedunculated and inward cupping of rete ridges is not characteristic [14]. CA tend to be larger in size, more often to occur in multiples, and are usually found in adults [14, 22].

Verrucous hyperplasia/carcinoma (VH/C) are premalignant and malignant variants of squamous cell carcinoma respectively [23]. While they may impart a verrucous appearance clinically, these neoplasms are not HPV-related [23]. They tend to be poorly defined, larger in size than HPV-related lesions, and associated with sites of smokeless tobacco placement or, in instances of proliferative verrucous leukoplakia, an elderly female demographic [23]. Histologically, VH/C are characterized by verrucous architecture and deceptively bland cytology [23]. In VCs, the rete ridges exhibit downward growth and push into the underlying connective tissues [23]. No central cupping is apparent; however, keratin spires may be present [23]. Features associated with malignancy, including increased mitotic activity, cellular pleomorphism, and paradoxical maturation, are absent [23]. The lack of these findings attributes to the potential confusion with benign entities such as VV [23].

Squamous Papilloma

SP is a common lesion and the most frequent benign oral epithelial entity in both children and adults [15, 24, 25]. In a large study of consecutive oral examinations of Army inductees, SP was the second most commonly encountered pathologic entity overall [26]. Adults experience the highest incidence, with increases between the third and seventh decades [13, 27]. The palate and tongue are most commonly affected, but any site may be involved [13, 27].

Clinically, SP is characterized by exophytic projections described as "finger-like" (Table 2; Fig. 3) [13, 27]. "Cauliflower" or "warty" are also common surface descriptors [13, 27]. SPs are usually pedunculated, with color ranging from

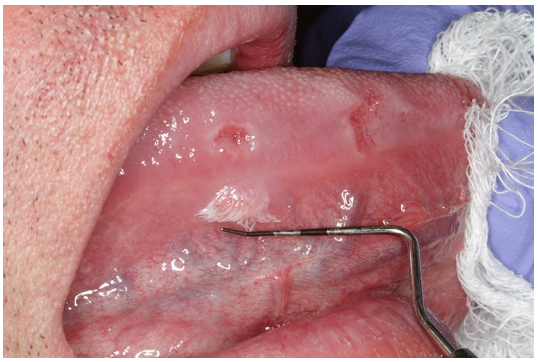

Fig. 3 Clinical image of squamous papilloma. Note the "finger-like" fronds. *Photograph courtesy of Dr. Brenda Nelson*

white to pink/red (Table 2) [13, 27]. The lesions are rarely larger than 5 millimeters in greatest dimension and usually solitary [27]. In a study of 205 SPs, only four patients had two simultaneous lesions [27].

Histologically, the exophytic and papillary architecture is appreciated at low power (Table 2; Fig. 4a) [14, 28]. In a fortuitous section, a stalk is appreciated. More often, the stalk is suggested by the vacant space between papillomatous fronds and underlying normal epithelium and connective tissues. Fronds of richly vascular connective tissue are surfaced by bland epithelium with varying degrees of keratinization (Fig. 4b, c) [13, 14, 28]. Scattered basilar or parabasilar mitotic figures are present, but without atypical forms (Fig. 4c) [23, 29]. Koilocytes are often identified within the upper spinous layers [29].

The clinical and histologic differential diagnosis for SP includes VV, VX, CA, giant cell fibroma (GCF), and papillary squamous cell carcinoma (P-SCC). Whereas VV is sessile and shows inward cupping of rete ridges, SP is usually pedunculated with a stalk [13, 18]. Furthermore, prominent granular cell layers and "church spire" keratinization are not characteristic of SP [13, 14]. The xanthoma cells and orange parakeratin of a VX are also absent [21]. CA tend to be larger than SP and are more frequently found in multiples [14].

The bosselated or papillary surface of a GCF attributes to approximately 28% of these lesions being clinically

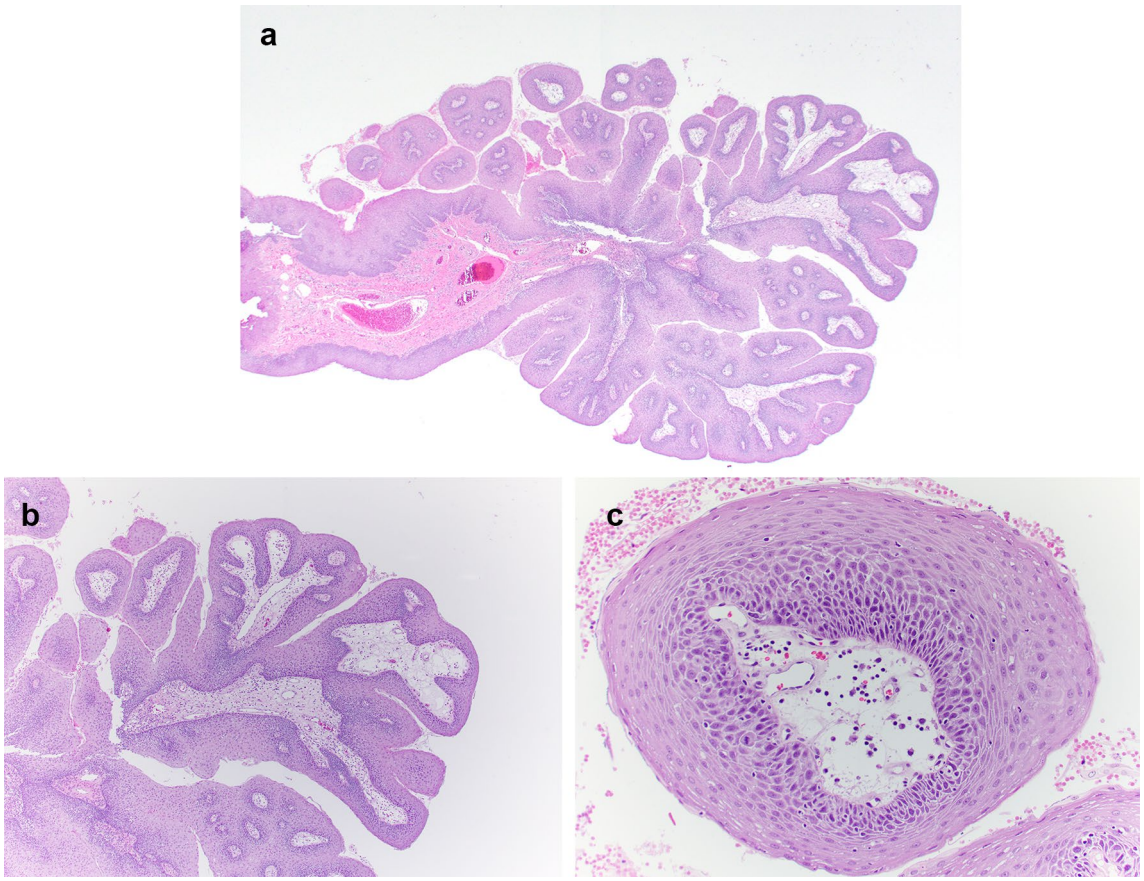

Fig. 4 Histologic features of squamous papilloma. **a** The exophytic nature is appreciated at low power. A stalk connects the lesional proliferation to the underlying normal tissues. **b** Medium power shows fronds comprising loose vascular connective tissue and surfaced by bland epithelium. **c** Normal epithelial maturation with a few scattered mitotic figures is apparent at high power

diagnosed as SP [30]. GCFs occur over a wide age range and are most common on the gingiva [30]. Histologically, the two entities are easily distinguished as SP is an epithelial proliferation whereas GCF is fibrous in nature [14, 30]. GCFs comprise loose connective tissue containing large and stellate multinucleated fibroblasts [30]. The surface epithelium is characterized by thin and elongated rete ridges [30].

The clinical and histologic presentation of P-SCC, a rare variant of squamous cell carcinoma, may mimic that of SP [23, 31, 32]. This variant is most common in the larynx, but may also affect additional sites of the upper aerodigestive tract including the oral cavity, especially the gingiva [23, 31]. In a study of 61 gingival P-SCC, 8% (5/61) were clinically diagnosed as SP [31]. Some literature reports P-SCC of the oral cavity to be associated with smoking and alcohol intake, with unclear associations with transcriptionally active HPV [23, 31, 32]. In another study that compared oral SP and P-SCC, no statistical difference in smoking or alcohol use was observed between the two patient groups [28]. Advanced age (≥60 years) and gingival site were risk factors associated with P-SCC as compared to SP [28].

On pathologic examination, this malignancy displays papillary growth with exophytic fronds and fibrovascular cores and/or broad, bulbous and rounded projections with less conspicuous fibrovascular cores [23]. P-SCC is separated into keratinizing and non-keratinizing histologic categories [23]. A full thickness epithelium comprising immature, basaloid cells with malignant cytology surfaces fibrovascular cores of the non-keratinizing P-SCC [23]. Keratinizing P-SCC displays any amount of mature squamous cells with minimal surface parakeratinization [23]. Features of malignancy including pleomorphism and disordered maturation are present [23, 28, 32]. The majority of oral cavity P-SCC are keratinizing but both variants are reported in this location [23]. Invasion past the basement membrane in either presentation may not be appreciated, leading to the potential to mistake these lesions for benign entities such as SP [23]. The lack of maturation and malignant cytologic features differentiate non-keratinizing P-SCC from SP [23, 32].

Condyloma Acuminatum

CA usually presents as anogenital warts and is the most commonly reported sexual transmitted infection in the United Kingdom and United States [33, 34]. These lesions are uncommon, however, in the oral cavity [22]. While the presence of simultaneous lesions of the genitalia and oral cavity suggests sexual transmission, additional routes of infection, such as through fomites, is possible [15, 22]. Adults are most commonly affected, with peaks in the third and fourth decades of life [22, 34, 35].

Clinically, CA may present as a solitary lesion or in multiples, some of which may coalesce to form larger growths (Table 2; Fig. 5) [14, 36]. In a study of 101 oral CA, 61% of patients experienced greater than five lesions [34]. The lesions may be pedunculated but are more often sessile, with cauliflower-like or moruloid surface texture and pink to white coloration (Fig. 5) [34, 36]. The tongue and upper lip are the most common intraoral locations [37].

Microscopically, lesions exhibit an exophytic, papillary architecture and broad base (Table 2; Fig. 6a) [14, 22]. The epithelium is moderately to markedly acanthotic with bulbous rete ridges [22, 35]. Thick, parakeratosis is often identified, with invaginations that fill the crypts between papillae (Fig. 6b) [14, 22]. Koilocytes are appreciated in the upper spinous layer (Fig. 6c) [22, 36].

CA usually occurs in multiples, but since they may also occur as a solitary lesion, the differential diagnosis includes entities of both presentations. Previously discussed lesions, such as SP, VX, and P-SCC may be considered, as well as MEH.

SP is smaller, solitary, and usually pedunculated [14]. VX may be clinically equivalent in size and similar in color, but histologic features of orange parakeratin plugging of crypts and xanthoma cells are distinctive [21].

P-SCC may be a difficult distinction from CA. Both entities share a predominantly exophytic and papillary architecture and overlap in size [22, 28, 31]. A gingival location in a patient of advanced age is more characteristic of P-SCC, whereas CA is most common on the tongue and lip of adults in their third to fourth decades of life [22, 28, 31]. P-SCC demonstrates immature basaloid cells or dysplastic squamous cells, which is the more common histologic type to the oral cavity [23, 32]. The presence of invasion definitively separates these entities; however this may be difficult to demonstrate in select sections, and, furthermore, some P-SCCs may be entirely intraepithelial [23]. In absence of demonstrated invasion, the malignant cytologic features of P-SCC separates these entities [23].

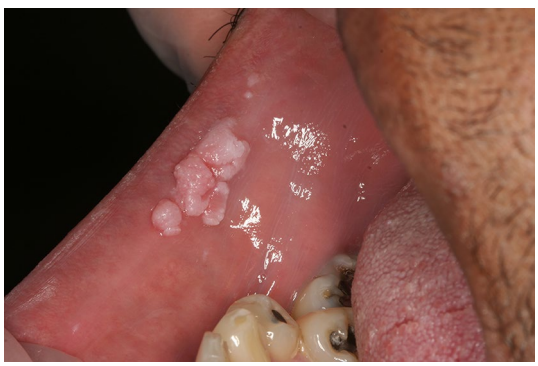

Fig. 5 Clinical image of condyloma acuminata. Note some of the lesions coalesce. A "cauliflower" surface texture is appreciated. *Photograph courtesy of Dr. Susan Muller*

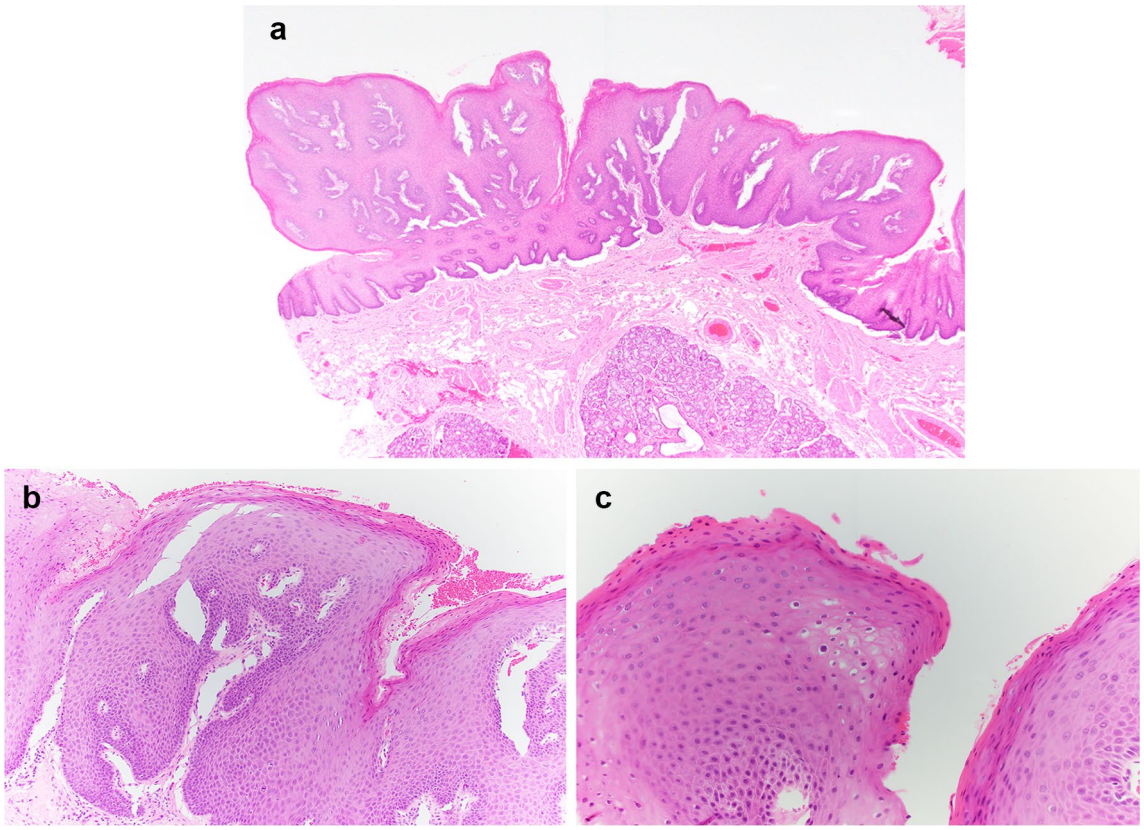

Fig. 6 Histologic features of condyloma acuminatum. **a** Low power demonstrates an exophytic lesion with marked acanthosis as compared to the normal epithelium (far left). **b** Parakeratin invaginations are seen between papillae. **c** Koilocytes, with clear halos around a shrunken nuclear, are seen in the upper spinous layer

In instances of multiple or confluent CA, MEH may be considered. MEH is most common in children and affects broader sites, while CA is more common in adults [22, 38]. Histologically, the mitosoid bodies characteristic of MEH are absent in CA [38].

Multifocal Epithelial Hyperplasia (Heck's Disease)

While MEH was initially documented in Latin-American populations, the first English publication on this entity described these lesions in Navajo and Alaskan Eskimo children [38, 39]. Interestingly, a report of similar lesions of indigenous people of Greenland dates to the 1800s [38]. Since these early findings, cases have been reported around the globe and across demographics, to include elderly and AIDS patients; but the disease remains most common in indigenous children in the Americas [38, 40]. In Eskimos, the prevalence ranges from 7 to 36%, and in the Waimiri-Atroari Indians of Brazil, the prevalence is up to 21% [40]. Females are significantly more affected than males, with ratios up to 5:1 [40].

Human leukocyte antigen subtype HLA-DR4 has been associated with genetic susceptibility to the disease [18, 41]. This finding may explain the increased prevalence in endemic areas as well as the tendency to affect multiple members of a family [42]. It is theorized that the DRB1*0404 molecule may not have sufficient binding affinity for HPV-13 or 32 peptides, increasing the susceptibility to infection [41].

The presence of multiple lesions, ranging in size and affecting various sites, is characteristic [39, 40]. In a study of 110 patients in Guatemala City, only three patients (2.8%) presented with a sole site affected, but multiple lesions were present at the site [38]. Two clinical presentations are described: the more common papulonodular variant and a papillomatous presentation [38, 40]. The papulonodular lesions tend to occur on the buccal and labial mucosa and are mucosa-colored and flat [40]. Those of the papillomatous presentation occur more often on the masticatory mucosa of the tongue and gingiva, with white and pebbly surfaces (Table 2; Fig. 7) [40]. Lesions of both variants range in size from 1 mm to 1 cm, often with coalescence [40]. Occurrences on the palate are rare and the floor of mouth is spared [38, 39].

Histologic examination reveals exophytic areas with nodular to papillary surface architecture (Table 2; Fig. 8a)

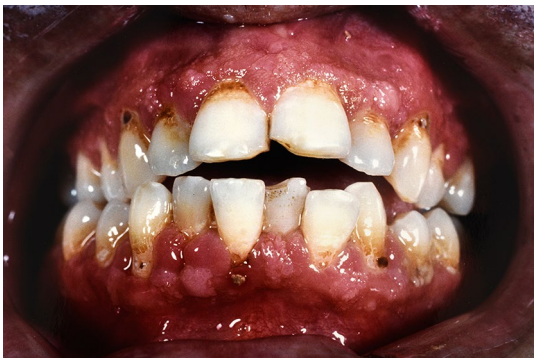

Fig. 7 Clinical image of multifocal epithelial hyperplasia. The lesions are generalized across the gingiva of both arches. Some individual lesions demonstrate a pebbly surface texture, while others show exophytic fronds. This variant is best described as "papillomatous". *Photograph courtesy of Dr. Brenda Nelson*

[39, 40]. The epithelium is acanthotic with widened and anastomosing rete ridges [38, 40]. Occasional mitosoid bodies, present in enlarged epithelial cells, show patterns of degenerating chromatin that may mimic mitotic figures (Fig. 8b) [38, 40]. These mitosoid bodies, in combination with kiolocytosis, demonstrate the viral cytopathic effects (Fig. 8b, c) [40]. The histologic findings are often subtle and may take a discerning eye, multiple sections, and correlating clinical history to arrive at the correct diagnosis [40].

The diagnosis is often suggested by the demographic and clinical findings; however, since children are primarily affected and multiple sites are involved, syndromes such as Cowden syndrome (CS), neurofibromatosis type 1 (NF1), or multiple endocrine neoplasia type 2B (MEN2B) may enter the differential diagnosis, particularly for the papulonodular variant. CS and NF1 have cutaneous manifestations, trichilemmomas of the face and café-au-lait spots respectively, as well as additional systemic manifestations [43, 44]. In MEN2B, oral neuromas may be the earliest evident clinical manifestation, although many children also experience constipation [45]. A biopsy definitively determines the etiology. A lesion of CS will histologically demonstrate a hamartomatous proliferation without viral cytopathic effects [43]. The neurofibromas of NF1 show spindled, comma-shaped Schwann cells admixed with fibroblasts, while the lesions of MEN2B show hyperplastic nerve bundles with perineural thickening [44, 45].

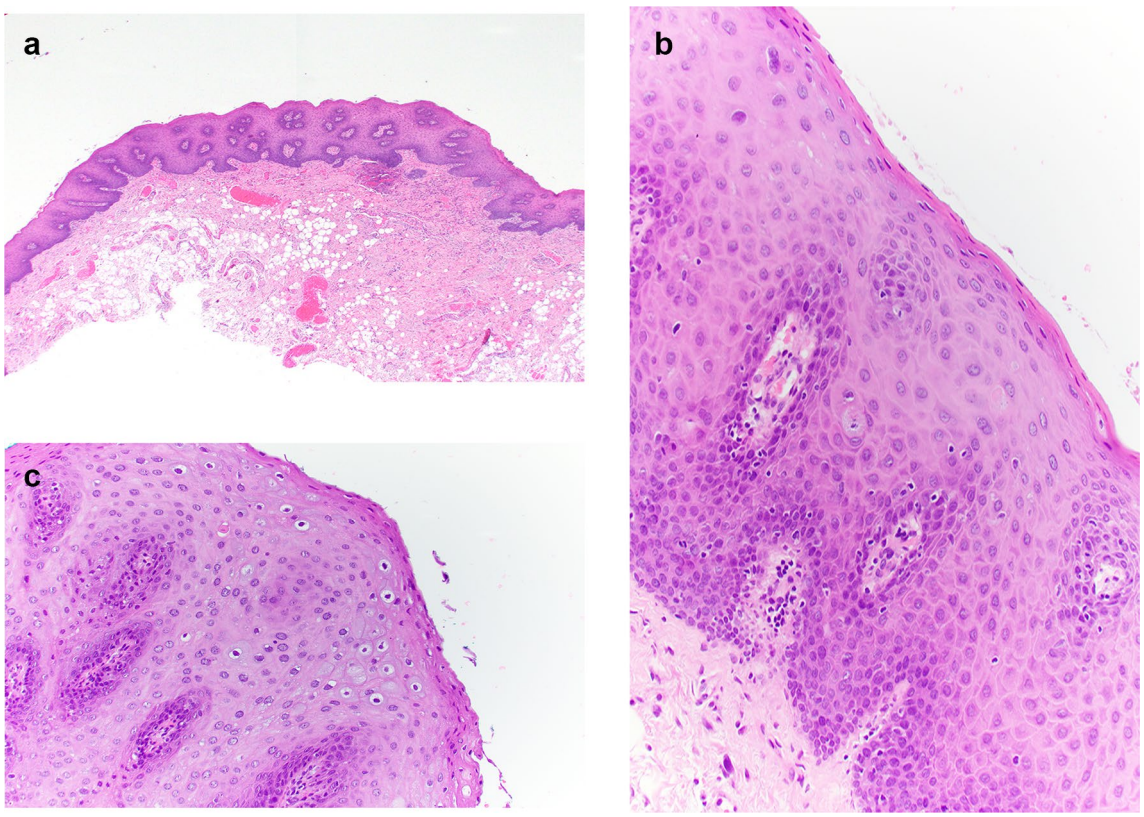

Fig. 8 Histologic feature of multifocal epithelial hyperplasia. **a** Low power demonstrates acanthotic, anastomosing rete ridges and a papillary surface. **b** A mitosoid body, with cellular ballooning and degenerating chromatin, is appreciated at medium power (center). **c** Scattered koilocytes are present at medium power

CA may also be considered; however, the demographics help differentiate these entities. Furthermore, the lesions of MEH are usually more numerous and the presentation more generalized [22, 39].

Management

Resolution without treatment is documented in HPV-related lesions, particularly cutaneous VV, anogential warts, and MEH [16]. In cutaneous VV, 40% of lesions in children resolve within a 2 year time frame, and in MEH the average time to regression is 18 months [16, 41]. Although HPV lesions may regress without intervention, biopsy is necessary for precise diagnosis. Furthermore, management is desired to decrease viral transmissibility and remove unsightly or bothersome lesions [18]. In instances of VV, SP, and CA, a surgical excisional biopsy is curative, with low instances of lesional recurrence [13, 18]. Lesional excision or destruction using CO_2 laser, electrosurgery, or cryotherapy are additional options, although these methods often induce artifactual changes that compromise the diagnostic capabilities of the pathologist [18]. The use of pharmacologic agents, such as phodophyllum, cidofovir, cimetidine, or imidazolquinoline, is not well-studied in the oral cavity, although case reports tout their success [46, 47].

Discussion

The benign HPV lesions are among the most common oral lesions [24]. Interestingly, although both SP and CA are caused by HPV 6 and 11 subtypes, they are distinct entities in head and neck literature due to differences in clinical and histologic presentations [18, 24]. This is in contrast to genitourinary pathology, where "squamous papilloma" designates a lesion unrelated to HPV [48].

Common oral pathology texts refer to CA as a sexually transmitted infection, while this distinction is absent for SP. This may cause confusion to the clinician, especially with pediatric patients where the presence of an HPV-related lesion may infer sexual abuse. Since it is known that HPV 6 and 11 may be sexually transmitted, the discovery of a lesion of either presentation raises concern [16]. It is important to remember, however, that other modes of transmission are possible [15, 16]. Even at anogential sites, recent studies have found a minority of these lesions to be caused by sexual abuse, with likelihood of abuse increasing with the age of the child [16, 49].

The American Academy of Pediatrics gives recommendations on evaluating these lesions and interviewing children and caregivers in the reports "Venereal warts in children" and "The evaluation of children in the primary care setting when sexual abuse is suspected" [49, 50]. In the United States and Canada, all healthcare professionals are mandated to report suspected child abuse to the appropriate agencies, which vary by state/providences. It is emphasized that an oral HPV lesion does not in-and-of-itself indicate sexual abuse. When confronted with this difficult scenario, providers are required to use their clinical evaluation skills, knowledge of disease etiology, and professional judgement to protect both children and innocent families.

While SP and CA are benign, a large Danish study found the presence of genital warts to be a significant risk factor for the development of HPV-related cancers, including those of the head and neck [51]. In men, the standardized incidence ratio (SIR) of genital warts to the development of HPV-related head and neck cancer was 3.5, and in females it was 4.8 [51]. This is likely due to increased risk of exposure to HR- HPV types, as early age of sexual exposure, multiple sexual partners, and having partners with multiple partners are risk factors for contraction of both HR- and LR-HPV types [7, 51].

The HPV vaccines are preventative to infection [52]. The bivalent HPV vaccine protects against high-risk types 16 and 18, and both the quadrivalent (4vHPV) and nonavalent HPV (9vHPV) vaccines protect against low-risk types 6 and 11 additionally [52, 53]. The 4vHPV vaccine was first licensed and available in the US in 2006, and the 9vHPV vaccine became available in the US in 2014 [52, 53]. Effectiveness of the vaccination programs is proven, with prevalence of HPVs 6/11/16/18 reduced by 89% in vaccinated populations within 6 years of 4vHPV vaccine availability [52]. Unvaccinated populations also experienced a drop, potentially reflecting early herd immunity [53]. Further illustrative, in countries with high vaccination rates, the prevalence and incidence of genital warts decreased approximately 50% year over year in women under 21 years [52]. While a thorough review of the efficacy of these vaccines in reducing the benign lesions of the oral cavity is lacking, preliminary evidence shows the trends will follow those of the genital lesions [53].

Interestingly, although the vaccines do not protect for HPV 2, 4, 13, or 32, several case reports document resolution of VV and MEH after vaccination [54]. The induction of anti-HPV immunoglobulins, cytotoxic T-lymphocytes, and cross-protection due to homologous sequences seems to play a role in clearance of the virus and lesional resolution [54].

The Center for Disease Control (CDC) recommends two vaccine doses taken 6–12 months apart for all children ages 11–12 and 3 doses over the course of 12 months for teens over 14 years [35]. The US Department of Health and Human Services' Healthy People initiative set a target for 80% of male and female adolescents to complete the HPV vaccine schedule by the year 2020 [55]. In 2017, less than half (48.6%) of adolescents completed their vaccines in the US [56]. The current worldwide coverage is

estimated at 6.1% in females [56]. Some reasons for these low statistics include distrust of institutions including the pharmaceutical industry as well as a concept of "risk compensation", or the unsubstantiated view that the vaccine might increase risky sexual behaviors [56]. Despite these barriers, studies show that one of the strongest predictors of both vaccine initiation and completion is a recommendation from a healthcare provider [56].

Although not currently included in the CDC recommendations, adults may still benefit from vaccination [57]. In October 2018, the Food and Drug Administration approved a supplemental application for use of the 9vHPV vaccine in adults ages 27–45 [57]. This measure recognizes the evidence for the vaccine to reduce HPV pathologies including warts, precancerous, and cancerous lesions [57].

Conclusions

The benign HPV-related lesions of the oral cavity differ in clinical and histologic presentations with some overlap. Both virus-associated and non-associated, malignant and benign entities may enter the differential diagnosis. As the clinical presentation and demographics are suggestive, clinicopathologic correlation is helpful, and sometimes necessary, to arrive at the correct diagnosis.

Although HPV may be sexually transmitted, it is important for care providers to recognize that other modes of transmission are possible [15, 16]. Clinical presentation, knowledge of the disease pathophysiology, thorough assessments, and clinical judgement must be utilized in assessing these lesions, especially in children.

HPV vaccination is proven to be effective, with preliminary evidence showing reduction in infections of the head and neck [56]. Evidence shows that recommendations from a healthcare providers are one of the strongest predictors to vaccine initiation and completion [56]. Healthcare professionals, including primary care providers, ear nose and throat specialists, and dentists, have a responsibility to educate their patients and recommend HPV vaccination.

Disclaimer The opinions and assertions expressed herein are those of the author and are not to be construed as official or representing the views of the Department of the Navy or the Department of Defense.

Funding No funding was received in association with this article.

Compliance with Ethical Standards

Conflict of interest Sasha J. Betz declares that she has no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Graham SV. The human papillomavirus replication cycle, and its links to cancer progression: a comprehensive review. Clin Sci (Lond). 2017;131(17):2201–21.
2. Egawa N, Egawa K, Griffin H, Doorbar J. Human papillomaviruses; epithelial tropisms, and the development of neoplasia. Viruses. 2015;7(7):3863–90.
3. Doorbar J, Egawa N, Griffin H, Kranjec C, Murakami I. Human papillomavirus molecular biology and disease association. Rev Med Virol. 2015;25(Suppl 1):2–23.
4. Tam S, Fu S, Xu L, et al. The epidemiology of oral human papillomavirus infection in healthy populations: a systematic review and meta-analysis. Oral Oncol. 2018;82:91–9.
5. Sabeena S, Bhat P, Kamath V, Arunkumar G. Possible non-sexual modes of transmission of human papilloma virus. J Obstet Gynaecol Res. 2017;43(3):429–35.
6. Summersgill KF, Smith EM, Levy BT, Allen JM, Haugen TH, Turek LP. Human papillomavirus in the oral cavities of children and adolescents. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001;91(1):62–9.
7. D'Souza G, Agrawal Y, Halpern J, Bodison S, Gillison ML. Oral sexual behaviors associated with prevalent oral human papillomavirus infection. J Infect Dis. 2009;199(9):1263–9.
8. Stanley MA. Epithelial cell responses to infection with human papillomavirus. Clin Microbiol Rev. 2012;25(2):215–22.
9. Bordignon V, Di Domenico EG, Trento E, et al. How human papillomavirus replication and immune evasion strategies take advantage of the host DNA damage repair machinery. Viruses. 2017;9(12).
10. Westrich JA, Warren CJ, Pyeon D. Evasion of host immune defenses by human papillomavirus. Virus Res. 2017;231:21–33.
11. Grabowska AK, Riemer AB. The invisible enemy—how human papillomaviruses avoid recognition and clearance by the host immune system. Open Virol J. 2012;6:249–56.
12. Lingen MW, Xiao W, Schmitt A, Jiang B, et al. Low etiologic fraction for high-risk human papillomavirus in oral cavity squamous cell carcinomas. Oral Oncol. 2013;49(1):1–8.
13. Abbey LM, Page DG, Sawyer DR. The clinical and histopathologic features of a series of 464 oral squamous cell papillomas. Oral Surg Oral Med Oral Pathol. 1980;49(5):419–28.
14. Eversole LR. Papillary lesions of the oral cavity: relationship to human papillomaviruses. J Calif Dent Assoc. 2000;28(12):922–7.
15. Syrjänen S. Human papillomavirus infections and oral tumors. Med Microbiol Immunol. 2003;192(3):123–8.
16. Mammas IN, Sourvinos G, Spandidos DA. Human papilloma virus (HPV) infection in children and adolescents. Eur J Pediatr. 2009;168(3):267–73.
17. Plasencia JM. Cutaneous warts: diagnosis and treatment. Prim Care. 2000;27(2):423–34.
18. Pringle GA. The role of human papillomavirus in oral disease. Dent Clin N Am. 2014;58(2):385–99.
19. Eversole LR, Laipis PJ, Green TL. Human papillomavirus type 2 DNA in oral and labial verruca vulgaris. J Cutan Pathol. 1987;14(6):319–25.
20. Fatahzadeh M. Oral manifestations of viral infections. Atlas Oral Maxillofac Surg Clin N Am. 2017;25(2):163–70.
21. Tamiolakis P, Theofilou VI, Tosios KI, Sklavounou-Andrikopoulou A. Oral verruciform xanthoma: report of 13 new cases and review of the literature. Med Oral Patol Oral Cir Bucal. 2018;23(4):e429–35.
22. Eversole LR, Laipis PJ, Merrell P, Choi E. Demonstration of human papillomavirus DNA in oral condyloma acuminatum. J Oral Pathol. 1987;16(5):266–72.

23. Wenig BM. Squamous cell carcinoma of the upper aerodigestive tract: dysplasia and select variants. Mod Pathol. 2017;30(s1):112–8.
24. Esmeili T, Lozada-Nur F, Epstein J. Common benign oral soft tissue masses. Dent Clin N Am. 2005;49(1):223–40.
25. Sato M, Tanaka N, Sato T, Amagasa T. Oral and maxillofacial tumours in children: a review. Br J Oral Maxillofac Surg. 1997;35(2):92–5.
26. Knapp MJ. Oral disease in 181,338 consecutive oral examinations. J Am Dent Assoc. 1971;83(6):1288–93.
27. Frigerio M, Martinelli-Kläy CP, Lombardi T. Clinical, histopathological and immunohistochemical study of oral squamous papillomas. Acta Odontol Scand. 2015;73(7):508–15.
28. Bao Z, Yang X, Shi L, Feng J, Liu W, Zhou Z. Clinicopathologic features of oral squamous papilloma and papillary squamous cell carcinoma: a study of 197 patients from eastern China. Ann Diagn Pathol. 2012;16(6):454–8.
29. Carneiro TE, Marinho SA, Verli FD, Mesquita AT, Lima NL, Miranda JL. Oral squamous papilloma: clinical, histologic and immunohistochemical analyses. J Oral Sci. 2009;51(3):367–72.
30. Houston GD. The giant cell fibroma. A review of 464 cases. Oral Surg Oral Med Oral Pathol. 1982;53(6):582–7.
31. Fitzpatrick SG, Neuman AN, Cohen DM, Bhattacharyya I. Papillary variant of squamous cell carcinoma arising on the gingiva: 61 cases reported from within a larger series of gingival squamous cell carcinoma. Head Neck Pathol. 2013;7(4):320–6.
32. Mehrad M, Carpenter DH, Chernock RD, et al. Papillary squamous cell carcinoma of the head and neck: clinicopathologic and molecular features with special reference to human papillomavirus. Am J Surg Pathol. 2013;37(9):1349–56.
33. Lacey CJ, Lowndes CM, Shah KV. Chapter 4: Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. Vaccine. 2006;24(Suppl 3):3/35–41.
34. Panici PB, Scambia G, Perrone L, et al. Oral condyloma lesions in patients with extensive genital human papillomavirus infection. Am J Obstet Gynecol. 1992;167(2):451–8.
35. Zunt SL, Tomich CE. Oral condyloma acuminatum. J Dermatol Surg Oncol. 1989;15(6):591–4.
36. Kui LL, Xiu HZ, Ning LY. Condyloma acuminatum and human papilloma virus infection in the oral mucosa of children. Pediatr Dent. 2003;25(2):149–53.
37. Squires J, Persaud DI, Simon P, Sinn DP. Oral condylomata in children. Arch Pediatr Adolesc Med. 1999;153(6):651–4.
38. Carlos R, Sedano HO. Multifocal papilloma virus epithelial hyperplasia. Oral Surg Oral Med Oral Pathol. 1994;77(6):631–5.
39. Archard HO, Heck JW, Stanley HR. Focal epithelial hyperplasia: an unusual oral mucosal lesion found in Indian children. Oral Surg Oral Med Oral Pathol. 1965;20:201–12.
40. Said AK, Leao JC, Fedele S, Porter SR. Focal epithelial hyperplasia—an update. J Oral Pathol Med. 2013;42(6):435–42.
41. Bennett LK, Hinshaw M. Heck's disease: diagnosis and susceptibility. Pediatr Dermatol. 2009;26(1):87–9.
42. García-Corona C, Vega-Memije E, Mosqueda-Taylor A, et al. Association of HLA-DR4 (DRB1*0404) with human papillomavirus infection in patients with focal epithelial hyperplasia. Arch Dermatol. 2004;140(10):1227–31.
43. Pilarski R, Burt R, Kohlman W, Pho L, Shannon KM, Swisher E. Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. J Natl Cancer Inst. 2013;105(21):1607–16.
44. Jett K, Friedman JM. Clinical and genetic aspects of neurofibromatosis 1. Genet Med. 2010;12(1):1–11.
45. Kahn MA, Cote GJ, Gagel RF. RET protooncogene mutational analysis in multiple endocrine neoplasia syndrome type 2B: case report and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996;82(3):288–94.
46. Patton LL. Oral lesions associated with human immunodeficiency virus disease. Dent Clin N Am. 2013;57(4):673–98.
47. Curi DS, Leite-Ribeiro PM, Torregrossa VR, Vieira VC, Sarmento VA. Efficacy of imidazolquinoline on treatment of condyloma acuminatum of the buccal mucosa. Spec Care Dent. 2017;37(1):51–4.
48. Cheng L, Leibovich BC, Cheville JC, et al. Squamous papilloma of the urinary tract is unrelated to condyloma acuminata. Cancer. 2000;88(7):1679–86.
49. Sinclair KA, Woods CR, Sinal SH. Venereal warts in children. Pediatr Rev. 2011;32(3):115–21. quiz 121.
50. Jenny C, Crawford-Jakubiak JE, Neglect, CoCAa, Pediatrics AAo. The evaluation of children in the primary care setting when sexual abuse is suspected. Pediatrics. 2013;132(2):e558–67.
51. Blomberg M, Friis S, Munk C, Bautz A, Kjaer SK. Genital warts and risk of cancer: a Danish study of nearly 50 000 patients with genital warts. J Infect Dis. 2012;205(10):1544–53.
52. Garland SM, Kjaer SK, Muñoz N, et al. Impact and effectiveness of the quadrivalent human papillomavirus vaccine: a systematic review of 10 years of real-world experience. Clin Infect Dis. 2016;63(4):519–27.
53. Guo T, Eisele DW, Fakhry C. The potential impact of prophylactic human papillomavirus vaccination on oropharyngeal cancer. Cancer. 2016;122(15):2313–23.
54. Cyrus N, Blechman AB, Leboeuf M, et al. Effect of quadrivalent human papillomavirus vaccination on oral squamous cell papillomas. JAMA Dermatol. 2015;151(12):1359–63.
55. Health.gov. Healthy People 2020. 2010. https://www.healthypeople.gov/search2/?query=human+papillomavirus+vaccine&op=Go. Accessed 15 Oct 2018.
56. Perez S, Zimet GD, Tatar O, Stupiansky NW, Fisher WA, Rosberger Z. Human papillomavirus vaccines: successes and future challenges. Drugs. 2018;78(14):1385–96.
57. Food and Drug Administration. FDA approves expanded use of Gardasil 9 to include individuals 27 through 45 years old. USDoHaH. 2018. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm622715.htm. Accessed 10 Oct 2018.