


REVIEW ARTICLE**VERRUCOUS PAPILLARY LESIONS OF ORAL MUCOSA- A REVIEW**Dushyantsinh Vala¹, Soumendu Bikash Maiti², Rajiv Ranjan², Amit Jain², Nehal Patel³¹Department of Oral Pathology, ²Department of Oral Medicine and Radiology, ³BDS Intern Darshan Dental College and Hospital, Udaipur, Rajasthan 31300**ABSTRACT:**

A variety of verrucous and papillary lesions affect the oral mucosa. Papillary lesions of the oral mucosa are characterized by focal, multifocal or diffuse exophytic growths with cauliflower or verrucous surface irregularity. This article is an attempt to provide a comprehensive review on different verrucous-papillary lesions affecting oral mucosa. We conclude by emphasizing on the need of microscopic examination in all instances and it must be coordinated with the clinical findings in order to allow for a definitive diagnosis.

Key words: Verrucous lesions, Papillary lesions, Oral mucosa

Corresponding Author: Dr. Dushyantsinh Vala, Department of Oral Pathology, Darshan Dental College and Hospital, Udaipur, Rajasthan 31300, India

This article may be cited as: Vala D, Maiti SB, Ranjan R, Jain A, Patel N. Verrucous papillary lesions of oral mucosa- A Review. J Adv Med Dent Scie Res 2016;4(6):52-67.

Access this article online	
Quick Response Code 	Website: www.jamdsr.com
	DOI: 10.21276/jamdsr.2016.4.6.14

INTRODUCTION:

During the course of an oral soft tissue examination we often discover mucosal nodules, and these common lesions are usually the fibromas. When found on the lower lip however, they may also be mucous extravasation phenomenon (mucoceles). Occasionally, mucosal nodules will exhibit a bosselated or cauliflower surface texture; or, indeed, some may have fingerlike projections.¹

Papillary lesions are those that are tumefactive with a cauliflower surface. Some are pedunculated others are sessile. Some are single; others are multiple or diffusely involve broad areas of the oral mucosa.¹ Papillary lesions of the oral mucosa are characterized by focal, multifocal or diffuse exophytic growths with cauliflower or verrucous surface irregularity. Depending upon the degree of surface keratinization they may appear white or coral pink. When the papillomas show minimal surface keratinization histologically, they appear pink, with the same coloration as normal mucosa. When surface hyperkeratosis is extant, the papillary lesions show a white surface.² When the clinical appearance is that of multiple projections or stalks, much like a sea anemone, they are usually said to be papillary; conversely, when the lesions are white and keratotic with a roughened surface, they are said to be verrucous. In the WHO classification of head and Neck Tumour – 2005 papillomas has been defined as “These form a range of localised hyperplastic exophytic and polypoid lesions of hyperplastic epithelium with a verrucous or cauliflower like morphology. Lesions of fibroepithelial hyperplasia are not generally included³.” Lesions with this appearance are comprised of individual disease entities of neo-plastic, inflammatory reactive hyperplastic, or genetic nature. The vast majority of papillomas are

associated with or indeed caused by members of the human papillomavirus (HPV) family, yet there are a few papillary growths that have not been associated with HPV. Because most papillary and verrucous lesions are of viral origin, they are transmissible. In general, oral mucosal papillomas are only mildly contagious and transmission requires direct mucosal contact. Viral transfer or inoculation to another individual probably requires an erosion or laceration of the recipient’s mucosal epithelium for virus to gain access to the basal cells of the stratified epithelium.¹ Microscopically the benign verrucae and papillomas show exophytic, fingerlike projections of stratified squamous epithelium, showing wide variations in the thickness of the keratin layer, which is usually parakeratinized.

The clinical appearance is often unique for a specific entity; however, most of these lesions share gross morphological features and a definitive diagnosis relies upon identification of microscopically evident architectural and cytological characteristics.³

CLASSIFICATION**1. Based on the type of the lesion¹¹(Regezi et al., 2003)**

- ❖ **Reactive/Infectious Lesions**
 - Squamous Papilloma
 - Papillary hyperplasia
 - Condyloma Latum
 - Condyloma Acuminatum
 - Focal Papillary Hyperplasia
- ❖ **Neoplasms**
 - Keratoacanthoma
 - Verrucous Carcinoma
- ❖ **Idiopathic Lesions**
 - Pyostomatitis Vegetans

- Verruciform Xanthoma

2. Based on the number and appearance of lesion (Eversol and Papanicolaou, 1983)

❖ **Focal Papillary and Verrucous Lesions of the Oral Mucosa**

- Squamous Papilloma
- Verruca Vulgaris
- Molluscum Contagiosum
- Verruciform Xanthoma
- Sialadenoma Papilliferum
- Keratoacanthoma
- Condyloma Acuminatum
- Squamous Cell Carcinoma
- Warty Dyskeratoma

❖ **Multifocal papillary and verrucous lesions of the oral mucosa**

- Papillary Hyperplasia
- Florid Papillomatosis
- Nevis Unis Lateris
- Verrucous Carcinoma
- Papillary Exophytic Squamous Cell Carcinoma
- Multiple Condylomata
- Focal Epithelial Hyperplasia
- Focal Dermal Hypoplasia Syndrome
- Multiple Hamartoma Syndrome
- Pyostomatitis Vegetans
- Acanthosis Nigricans
- Verruciform Leukoplakia
- Keratosis Follicularis

3. Based on the involvement of HPV as an etiological factor¹. (Eversole, 2000)

❖ **Human papilloma viruses and Head and Neck Lesions:**

Genotype	Disease
HPV 2, 4	Verruca vulgaris
HPV 6, 11	Condyloma Acuminatum squamous papilloma
HPV 13, 32	Focal epithelial hyperplasia
HPV 16	Proliferative verrucous leukoplakia subtypes
HPV 6, 11, 16	Verrucous carcinoma
HPV 16, 18	Squamous cell carcinoma

❖ **Papillary Oral Lesions without Known Viral Association**

- Papillary hyperplasia (Papillomatosis)
- Verruciform Xanthoma
- Cowden syndrome
- Nevus unius lateris
- Acanthosis Nigricans

4. Based on their malignant potential⁵ (Thomas and Barret, 2009).

❖ **BENIGN**

- Viral papillomas:
- Squamous papilloma; Verruca vulgaris; Condyloma acuminatum
- Focal epithelial hyperplasia (Heck's disease)
- Fibro-epithelial polyps
- Verruciform xanthoma
- Papillary hyperplasia
- Pyostomatitis vegetans
- Sialadenoma papilliferum
- Acanthosis nigricans
- Darier's disease

❖ **POTENTIALLY MALIGNANT**

- Verrucous hyperplasia
- Papillary dysplasia
- Proliferative (verrucous) leukoplakia

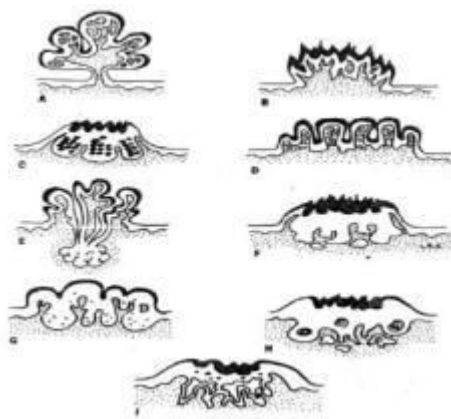
❖ **MALIGNANT**

- Verrucous carcinoma

- Papillary carcinoma:
- Non-invasive (synonymous with papillary dysplasia)
- Invasive (essentially a conventional squamous cell carcinoma requiring treatment as such)
- Carcinoma cuniculatum (essentially a conventional, well differentiated squamous cell carcinoma requiring treatment as such)

FOCAL PAPILLARY LESIONS:

Localized papillary growths are represented by viral and non-viral epithelial proliferations which may be pedunculated or sessile. Some of these lesions exhibit normal coloration while others are white. Rolled margins with a distinct collarette are observed in some of these lesions yielding a crateriform or umbilicated appearance while the umbilicated nodules are not always characterized by a surface papillary or verrucous appearance clinically, microscopic examination will disclose acanthotic in folding with keratin crypts. **Figure 1** illustrates the salient microscopic architectural features of these focal papillary lesions.



1. Squamous Papilloma (Figure 1A) 2. Verruca Vulgaris (Figure 1B)
 3. Molluscum Contagiosum (Figure 1C) 4. Verruciform Xanthoma (Figure 1D)
 5. Sialadenoma Papilliferum (Figure 1E) 6. Keratoacanthoma (Figure 1F)
 7. Condyloma Acuminatum (Figure 1G) 8. Squamous Cell Carcinoma (Figure 1H)
 9. Warty Dyskeratoma (Figure 1I)

SQUAMOUS PAPILOMA

The squamous papilloma is a benign proliferation of stratified squamous epithelium, resulting in a papillary or verruciform mass. The squamous papilloma is the most common benign epithelial neoplasm of oral epithelium.¹²

ETIOLOGY:

Presumably, this lesion is induced by the human papillomavirus (HPV).¹³ The exact mode of transmission is unknown. In contrast to other HPV induced lesions, the viruses in this lesion appear to have an extremely low virulence and infectivity rate. A latency or incubation period of 3 to 12 months has been suggested.¹⁴

CLINICAL FEATURES:

The squamous papilloma occurs with equal frequency in both men and women. Some authors have asserted that it develops predominantly in children, but epidemiologic studies indicate that it can arise at any age and, in fact, is diagnosed most often in persons 30 to 50 years of age. Sites of predilection include the tongue, lips, and soft palate, but any oral surface may be affected. This lesion is the most common of the soft tissue masses arising from the soft palate¹. The squamous papilloma is a soft, painless, usually pedunculated, exophytic nodule with numerous fingers like surface projections that impart a "cauliflower" or wartlike appearance (**Figure 2**).



Figure 2: (a) Clinical appearance¹ (b) gross specimen showing finger-like projections¹ (c) squamous papilloma in the palatal region¹¹

Projections may be pointed or blunted and the lesion may be white, slightly red, or normal in color, depending on the amount of surface keratinization. The papilloma is usually solitary and enlarges rapidly to a maximum size of about 0.5 cm, with little or no change thereafter. However, lesions as large as 3.0 cm in greatest diameter have been reported.¹³ It is sometimes difficult to distinguish this lesion clinically from verruca vulgaris, condyloma acuminatum, verruciform xanthoma or focal epithelial hyperplasia. In addition, extensive coalescing papillary lesions of the oral mucosa may be seen in several skin disorders, including nevus unius lateris, acanthosis nigricans, and focal dermal hypoplasia (Goltz Gorlin) syndrome. Laryngeal papillomatosis, a rare and potentially devastating disease of the larynx and hypopharynx, has two distinct types: (1) juvenile onset and (2) Adult onset. Hoarseness is the usual presenting feature, and rapidly proliferating papillomas in the juvenile-onset type may obstruct the airway.¹³

DIFFERENTIAL DIAGNOSIS:

The differential diagnosis of oral squamous papilloma, when solitary, includes verruciform xanthoma, papillary hyperplasia, and condyloma acuminatum. Verruciform xanthoma may resemble squamous papilloma, although this lesion has a distinct predilection for the gingiva and the alveolar ridge. A cause-and-effect relationship (e.g., lesion appearing under an ill fitting denture) should be evident for inflammatory papillary hyperplasia. The condyloma would be larger than the papilloma, would have a broader base, and would appear pink to red as a result of less keratinization¹¹.

DIAGNOSIS: It is based on

- Clinical appearance
- Biopsy features

HISTOPATHOLOGY¹:

The papilloma is characterized by a proliferation of keratinized stratified squamous epithelium arrayed in finger like projections with fibro vascular connective tissue cores (**Figure 3**).

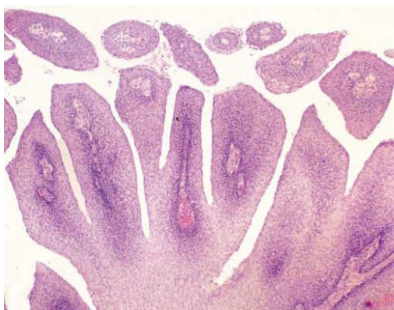


Figure 3: Moderately keratinized papilloma of verruca vulgaris type showing koilocytic change in the upper prickle cell layers¹.

The connective tissue cores may show inflammatory changes, depending on the amount of trauma sustained by the lesion. The keratin layer is thickened in lesions with a whiter clinical appearance, and the maturation pattern. Occasional papillomas demonstrate basilar hyperplasia and mitotic activity, which can be mistaken for mild epithelial dysplasia. Koilocytes, virus-altered epithelial clear cells with small dark (pyknotic) nuclei, are sometimes seen high in the prickle cell layer.¹³ **Dysplastic Oral Warts:** Some oral papillomas in patients with acquired immunodeficiency syndrome (AIDS) exhibit microscopic changes that are dysplastic in appearance. The degree of dysplasia ranges from mild to severe. The outcome, or natural history, of these dysplastic warts is unknown, although invasive carcinoma has yet to be reported despite several years of follow-up. A wide variety of HPV subtypes, including 16 and 18, can be demonstrated in these lesions.¹⁵

TREATMENT AND PROGNOSIS:

Conservative surgical excision, including the base of the lesion, is adequate treatment for the oral squamous papilloma, and recurrence is unlikely. Frequently, lesions have been left untreated for years with no reported transformation into malignancy, continuous enlargement, or dissemination to other parts of the oral cavity.¹⁴

VERRUCA VULGARIS

Verruca vulgaris is a benign, virus-induced, focal hyperplasia of stratified squamous epithelium. One or more of the associated human papillomavirus (HPV) types 2, 4, 6, and 11 are found in virtually all examples. Verruca vulgaris is contagious and can spread to other parts of a person's skin or mucous membranes by way of autoinoculation. It infrequently develops on oral mucosa but is extremely common on the skin.¹⁶

CLINICAL FEATURES:

Verruca vulgaris is frequently discovered in children, but occasional lesions may arise even into middle age. The skin of the hands is usually the site of infection. When the oral mucosa is involved, the lesions are usually found on the vermilion border, labial mucosa, or anterior tongue¹. Typically, the verruca appears as a painless papule or nodule with papillary projections or a rough pebbly surface (Figure 4).

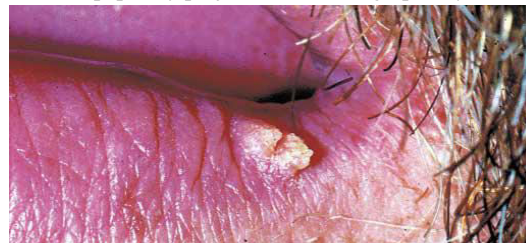


Figure 4: Clinical appearance of Verruca vulgaris¹¹

It may be pedunculated or sessile. Cutaneous lesions may be pink, yellow, or white; oral lesions are almost always white. Verruca vulgaris enlarges rapidly to its maximum size (usually less than 5 mm), and the size remains constant for months or years thereafter unless the lesion is irritated. Multiple or clustered lesions are common. On occasion, extreme accumulation of compact keratin may result in a hard surface projection several millimeters in height, termed a cutaneous horn or keratin horn. Other cutaneous lesions including seborrheic keratosis, actinic keratosis, and squamous cell carcinoma, may also create a cutaneous horn.¹⁴

DIFFERENTIAL DIAGNOSIS:

- Focal epithelial hyperplasia
- Keratoacanthoma
- Papillary squamous carcinoma
- Squamous papilloma
- Condyloma acuminatum

DIAGNOSIS: It is based on

- Clinical appearance
- Microscopic findings
- Immunohistochemical demonstration of HPV common antigen

Histopathology:

The verruca vulgaris is characterized by a proliferation of hyperkeratotic stratified squamous epithelium arranged into fingerlike or pointed projections with connective tissue cores chronic inflammatory cells often infiltrate the supporting connective tissue (Figure 5).

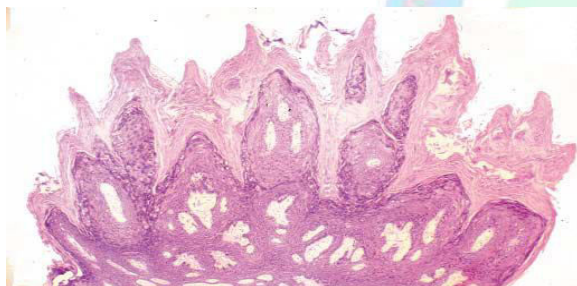


Figure 5: Microscopic appearance

Elongated rete ridges tend to converge toward the center of the lesion, producing a "cupping" effect. A prominent granular cell layer (hypergranulosis) exhibits coarse, clumped keratohyaline granules. Abundant koilocytes are often seen in the superficial spinous layer. Koilocytes are HPV-altered epithelial cells with perinuclear clear spaces and small, dark nuclei (pyknosis). Eosinophilic intranuclear viral inclusions are often noted within the cells of the granular layer.¹⁴

TREATMENT AND PROGNOSIS:

Skin verrucae are treated effectively by liquid nitrogen cryotherapy, conservative surgical excision or curettage, or topical application of keratinolytic agents (usually containing salicylic acid and lactic acid). Oral lesions are usually surgically excised, or they may be destroyed by laser, cryotherapy, or electrosurgery. Cryotherapy induces a subepithelial blister that lifts the infected epithelium from the underlying connective tissue, allowing it to slough away. All destructive or surgical treatments should extend to include the base of the lesion.¹⁴ **Recurrence** is seen in a small proportion of treated cases. Without treatment, verrucae do not transform into malignancy, and

two thirds will disappear spontaneously within 2 years, especially in children.¹⁶

MOLLUSCUM CONTAGIOSUM

Molluscum Contagiosum (MC) is a virus-induced epithelial hyperplasia produced by the molluscum contagiosum virus. At least 6% of the population (more in older age groups) has anti-bodies to this virus, although few ever develop lesions. After an incubation period of 14 to 50 days, infection produces multiple papules of the skin or, rarely, mucous membranes. These remain small for months or years and then spontaneously involute. During its active phase, the molluscum contagiosum virus is sloughed from a central core in each papule. **Routes of transmission** include sexual contact (in adults) and such nonsexual contacts (in children and teenagers) as sharing clothing, wrestling, communal bathing, and swimming. Lesions have a predilection for warm portions of the skin and sites of recent injury; flord cases have been reported in immunocompromised patients.¹⁷

ETIOLOGY:

MC has no animal reservoir, infecting only humans, as did smallpox. However, there are different pox viruses that infect many other mammals. The infecting human MC virus is a DNA poxvirus called the molluscum contagiosum virus (MCV). There are four types of MCV, MCV-1 to -4; MCV-1 is the most prevalent and MCV-2 is seen usually in adults and often sexually transmitted.¹⁸

CLINICAL FEATURES:

Molluscum contagiosum is usually seen in children and young adults. The papules almost always are multiple and occur predominantly on the skin of the neck, face (particularly eyelids), trunk, and genitalia. Infrequently, oral involvement occurs, usually on the lips, buccal mucosa, or palate.¹ Lesions are pink, smooth surfaced, sessile, nontender, and nonhemorrhagic papules that are 2 to 4 mm in diameter (Figure 6).



Figure 6: Molluscum contagiosum. Multiple facial skin lesions in an HIV-positive subject¹

The classic wart of molluscum is a crateriform papule, a small normal colored skin nodule with a depressed central pit. When present, MC lesions tend to be multiple. Many show a small central indentation or keratin-like plug from which a curdlike substance can be expressed. Some are surrounded by a mild inflammatory erythema and may be slightly tender. Multiple papillary lesions in a child should arouse suspicion of sexual abuse, warranting investigation of persons in contact with that child¹⁸.

HISTOPATHOLOGY:

Molluscum contagiosum appears as a localized lobular proliferation of surface stratified squamous epithelium (Figure 7a and b). The central portion of each lobule is filled with bloated keratinocytes that contain large, intra nuclear, basophilic viral inclusions called **molluscum bodies**¹ (Figure 7c).

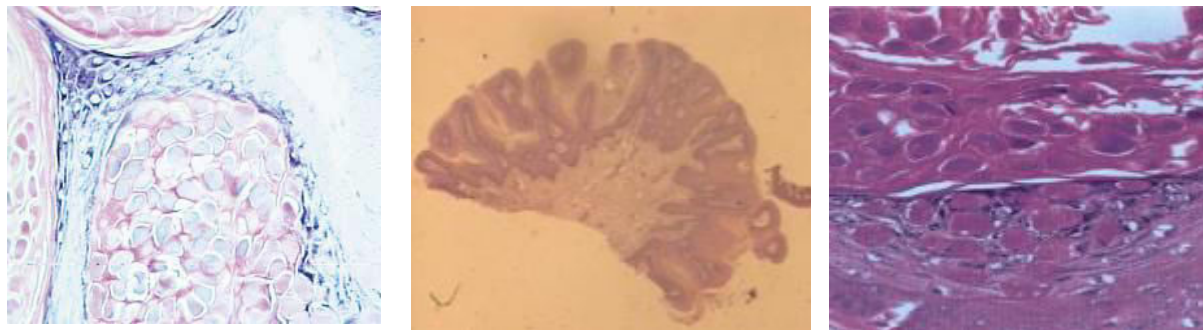


Figure 7: (a) Molluscum bodies representing huge viral inclusions in keratinocytes. (b) Well defined epidermal proliferation demonstrating craterlike depression filled with virally altered keratinocytes (c) Photomicrograph showing keratinocytes with large, basophilic viral inclusions (Molluscum bodies) being sloughed in to the central crater (top)¹.

These bodies begin as small eosinophilic structures in cells just above the basal layer. As they approach the surface, these bodies increase so much in size that they frequently become larger than the original size of the invaded cells. A central crater is formed at the surface as stratum corneum cells disintegrate to release their molluscum bodies. These unique features make the diagnosis readily apparent.

TREATMENT AND PROGNOSIS:

In most cases of molluscum contagiosum, spontaneous remission occurs within 6 to 9 months; however, curettage and cryotherapy are effective treatments for papules removed electively. Podophyllotoxin and t retinoin therapies are popular but less effective, and topical imiquimod, an immuneresponse modifier, recently has been shown to be effective in reducing or eliminating the lesions. There is no apparent potential to transform into carcinoma, and the lesions tend not to recur after treatment¹⁴.

VERRUCIFORM XANTHOMA

Verruciform xanthoma is a hyperplastic condition of the epithelium of the mouth, skin, and genitalia, with a characteristic accumulation of **lipid-laden histiocytes** beneath the epithelium. First reported by **Shafer in 1971**, it remains largely an oral disease; its cause is still unknown. Although verruciform xanthoma is a papillary lesion, human **papillomavirus doesnot appear to play a role** in its pathogenesis. The lesion probably represents an unusual reaction or immune response to localized epithelial trauma or damage. This hypothesis is supported by cases of verruciform xanthoma that have developed in association with disturbed epithelium (e.g., lichen planus, lupus erythematosus, epidermolysis bullosa, epithelial dysplasia, pemphigus vulgaris, warty dyskeratoma, graft-versushost disease)¹⁹. The lesion is histopathologically similar to other dermal xanthomas, but it is not associated with diabetes, hyperlipidemia, or any other metabolic disorder²⁰.

CLINICAL FEATURES

Verruciform xanthoma is typically seen in whites, 40 to 70 years of age. There is a strong female predilection (a 1: 2 male-to-female ratio). Approximately half of the intraoral lesions occur on the gingiva and alveolar mucosa, but any oral site may be involved. The lesion appears as a well-demarcated, soft, painless, sessile, slightly elevated mass with a white, yellow-white, or red color and a papillary or roughened (verruciform) surface (Figures 17a, b). Rarely, flat-topped nodules are seen without surface projections. Most lesions are smaller than 2 cm in greatest diameter; no oral lesion larger than 4 cm has been reported. Multiple lesions occasionally have been described. Clinically, verruciform xanthoma may be similar to squamous papilloma, condyloma acuminatum, or early carcinoma¹⁹.

Zegarelli et al., (1975) introduced the concept that local trauma and inflammation lead to epithelial entrapment and the cause of accumulation of lipid-containing macrophages is epithelial degeneration. The products of epithelial breakdown elicit an inflammatory response, which is manifested by a predominant neutrophilic infiltrate in the epithelium and a subsequent release of lipid material through the epithelium that finally is scavenged by the macrophages. Several authors have supported this theory. Zegarelli et al. suggested a “local irritant” as the initiator of this process. Discussing the epithelial hyperplasia with elongation of the epithelial rete ridges, Mostafa et al., (1993), suggested that this elongation is illusory and is not a proliferation of epithelial cells with downward growth of the retepegs, but rather results from the upward pushing effect of the accumulated macrophages towards the epithelium. This according to the authors reflects the thinning of the epithelium overlying the macrophages in the connective tissue papillae.¹⁴ Xanthomas of skin are usually associated with hyperlipoproteinemia accompanying atherosclerotic vascular disease, diabetes mellitus and familial lipoprotein disorders. No correlation with high blood lipids has been uncovered with regard to oral verruciform xanthoma.



Figure 8: Small approx. 0.5 x 0.5 cm, sessile cauliflower like growth seen in the lower anterior gingival region in between two central incisors¹⁹

DIFFERENTIAL DIAGNOSIS:

A differential diagnosis for this entity would include squamous papilloma, papillary squamous carcinoma, and condyloma acuminatum¹¹.

HISTOPATHOLOGY¹⁹

It demonstrates papillary, acanthotic surface epithelium covered by a thickened layer of parakeratin. On routine H & E staining, the keratin layer often exhibits a distinctive orange coloration. Clefts or crypts between the epithelial projections are filled with parakeratin, and reteridges are elongated to a uniform depth. The most important diagnostic feature is the accumulation of numerous large macrophages with foamy cytoplasm, which typically are confined to the connective tissue papillae (Figure 9). These foam cells, also known as xanthoma cells, contain lipid and periodicacid-Schiff (PAS) positive, diastase resistant granules. Immunohistochemically it is CD68 positive.

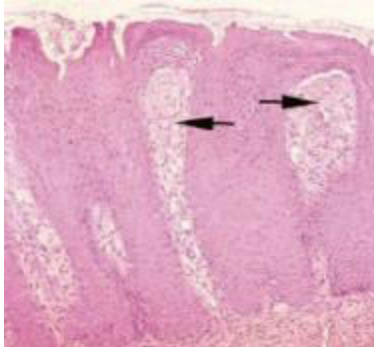


Figure 9: Photomicrograph showing bubbly foam or xanthoma cells in the connective tissue papillae between epithelial cells.

TREATMENT AND PROGNOSIS:

The verruciform xanthoma is treated with conservative surgical excision. Recurrence after removal of the lesion is rare, and no malignant transformation has been reported. However, two cases have been reported in which a verruciform xanthoma occurred in association with carcinoma in situ or squamous cell carcinoma. This does not necessarily imply that verruciform xanthoma is a potentially malignant lesion; however, it may indicate that hyperkeratotic or dysplastic oral lesions can undergo degenerative changes to form a verruciform xanthoma¹⁴.

SIALADENOMA PAPILLIFERUM

Abrams and Finck first used the term *sialadenoma papilliferum* in 1969 to describe 2 cases of an unusual neoplastic salivary gland proliferation. Slightly more than 50 cases have been reported in the English-language literature. Grossly, the neoplasm is a well-circumscribed, round-to-oval excrescence of the mucosal surface.²¹

CLINICAL FEATURES:

A benign neoplasm of excretory salivary duct epithelium, sialadenoma papilliferum resembles both clinically and histologically the eccrine skin tumor syringocystadenoma papilliferum. This rare salivary tumor is most often seen among elderly males on the palate and buccal mucosa. Clinically, the lesion is well demarcated and papillary with palpable indurations of the underlying sub-mucosa.²⁰

HISTOPATHOLOGY²¹

Histologically, collections of duct like spaces underlying a verrucous-like proliferation of squamous epithelium are seen. The ducts like structures are composed of tall columnar cells, and although they are the major cell type lining these ducts like spaces, goblet cells are also identified. It shows branching ductal structures that extend into the papillary mucosa above the level of the adjacent mucosa (Figure 11).

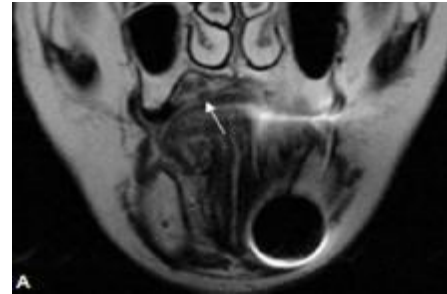


Figure 10: In preoperative MRI view, well demarcated firm mass was observed under the palatal mucosa (white arrow)²¹.

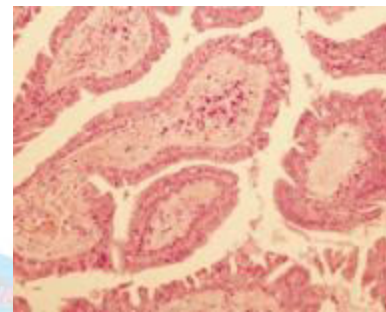


Figure 11: High magnification image of a region showing papillary projection. Papillary fronds were lined by a double row of cells composed of luminal columnar cells and short cuboidal or basaloid cells²¹. (Original magnification x200)

The surface is composed of papillary projections of surface stratified squamous epithelium with a parakeratin layer of variable thickness. This submucosal component is also papillary with nodular projections of ductal epithelium protruding into a tortuous cystic luminal cavity this ductal proliferation shows abrupt transition into stratified squamous epithelium that covers the mucosal papillae. The surface component evinces a transition into pseudostratified ductal eosinophilic columnar epithelium which extends into the underlying submucosa. The histogenesis of sialadenoma Papilliferum is still unclear. Some authors have suggested pluripotential myoepithelial cells as precursors of sialadenoma papilliferum and basal pluripotential cells. Since squamous differentiation is present, excretory ducts have also been implicated as the site of origin¹⁴.

TREATMENT

Surgical excision is the treatment of choice and the margins must be wide enough to include the underlying deep extensions²².

KERATOACANTHOMA

Keratoacanthoma is a self-limiting, epithelial proliferation with a strong clinical and histopathologic similarity to well-differentiated squamous cell carcinoma. In fact, some authorities consider it to represent an extremely well-differentiated form of squamous cell carcinoma. Cutaneous lesions presumably arise from the infundibulum of hair follicles. Intraoral lesions have been reported, but they are rare and, in fact, some authorities do not accept keratoacanthoma as an intraoral disease.²³ The cause of this lesion is unknown, but sun damage and human papillomavirus (HPV), possibly subtypes 26 or 37, have been proposed. The association with sun damage is suggested by the fact that most solitary lesions are found on sun-exposed skin, predominantly in the elderly. There appears to be a hereditary predisposition for multiple lesions, and the lesions occur with

increased frequency in immunosuppressed patients and those with **Muir-Torre syndrome** (sebaceous neoplasms, kerato-acanthomas, and gastrointestinal carcinomas).¹⁴

CLINICAL FEATURES

Keratoacanthoma rarely occurs in patients before 45 years of age and shows a male predilection. Almost 95% of solitary lesions are found on sun-exposed skin, and 8% of all cases are found on the outer edge of the vermilion border of the lips, with equal frequency on both the upper and lower lips.¹¹ Keratoacanthoma appears as a firm, nontender, well-demarcated, sessile, dome-shaped nodule with a central plug of keratin (**Figures 12**), although lesions reported as intraoral keratoacanthoma usually have lacked the central plug. The outer portion of the nodule has a normal texture and color but may be erythematous. The central keratin plug is yellowish, brown, or black and has an irregular, crusted, often verruciform surface.²³



Figure 12: Keratoacanthoma, This lesion, which is located at the outer edge of the vermilion border of the lip, demonstrates a prominent core or plug of keratin¹¹

The brown appearance is caused by extrinsic pigments that become incorporated with the excessive keratin. Intraoral KAs are generally nonpigmented. The peripheral mounded borders show an abrupt transition into normal skin or mucosa, both clinically and histologically.¹ Rapid enlargement is typical, with the lesion usually attaining a diameter of 1 to 2 cm within 6 weeks. This critical feature helps to distinguish it from the more slowly enlarging squamous cell carcinoma. Most lesions regress spontaneously within 6 to 12 months of onset, frequently leaving a depressed scar in the area.

Occasional patients demonstrate large numbers of keratoacanthomas. One multiple-lesion variant, the Ferguson Smith type, manifests in early life and appears to be hereditary; the lesions are not likely to involute spontaneously. Another variant manifests as hundreds of small papules of the skin and upper digestive tract (eruptive Grzybowski type) and may be associated with internal malignancy.¹⁴

DIFFERENTIAL DIAGNOSIS¹¹

- Squamous cell carcinoma
- Molluscum contagiosum
- Warty dyskeratoma
- Verruca vulgaris
- Pilomatricoma
- Condyloma acuminatum

DIAGNOSIS

- Clinical evaluation, follow-up
- Histopathology

HISTOPATHOLOGY²⁴

Keratoacanthoma of the skin and lip vermilion warrants excisional or large incisional biopsy with inclusion of adjacent, clinically normal epithelium for proper histopathologic interpretation; this is because the overall pattern of the tumor is diagnostically more important than the

appearance of individual cells. The cells appear mature, although considerable dyskeratosis (abnormal or premature keratin production) is typically seen in the form of deeply located individually keratinizing lesional cells and keratin pearls similar to those found in well differentiated squamous cell carcinoma.

The surface epithelium at the lateral edge of the tumor appears normal; at the lip of the central crater, however, a characteristic acute angle is formed between the overlying epithelium and the lesion. The crater is filled with keratin, and the epithelium at the base of the crater proliferate downward (**Figure 13**).

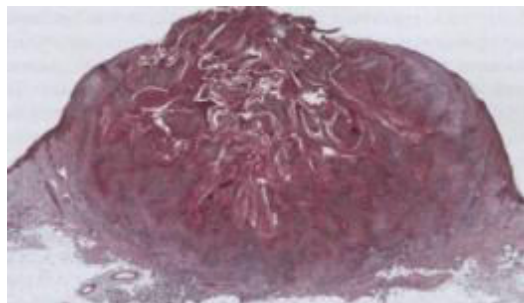


Figure 13: Keratoacanthoma. Low-power microscopic view showing extensive epidermal proliferation with a central keratin²⁴

This action often elicits a pronounced chronic inflammatory cell response. Downward proliferation does not extend below the level of the sweat glands in skin lesions or into underlying muscle in vermilion lesions. Late-stage lesions show considerably more keratinization of the deeper aspects of the tumor than do early lesions.²⁴

TREATMENT AND PROGNOSIS¹⁴

Despite the propensity of keratoacanthoma to involute of its own accord, surgical excision of large lesions is indicated for optimal aesthetic appearance because significant scarring may otherwise occur. After excision, 2% of treated patients experience recurrence. Aggressive behavior and malignant transformation into carcinoma have been reported in a small proportion of keratoacanthomas.

CONDYLOMA ACUMINATUM

Condyloma acuminatum is a virus-induced proliferation of stratified squamous epithelium of the genitalia, perianal region, mouth, and larynx. One or more of the HPV types 2, 6, 11, 53, and 54 are usually detected in the lesion. However, the high-risk types 16 and 18 also found with frequency, especially in anogenital lesions. Condyloma is considered to be a sexually transmitted disease (STD), with lesions developing at a site of sexual contact or trauma.²⁵

This lesion represents 20% of all STDs diagnosed in STD clinics and may be an indicator of sexual abuse when diagnosed in young children. It is not unusual for oral and anogenital condylomata to be present concurrently. The incubation period for a condyloma is 1 to 3 months from the time of sexual contact. Once present, auto-inoculation to other mucosal sites is possible.²⁵

CLINICAL FEATURES¹¹

Condylomata are usually diagnosed in **teenagers and young adults**, but people of all ages are susceptible. Oral lesions most frequently occur on the labial mucosa, soft palate, and lingual frenum. The typical condyloma appears as a sessile, pink, well-demarcated, nontender, exophytic mass with short, blunted surface projections (**Figure 14**).

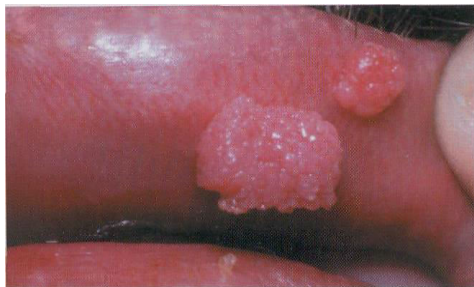


Figure 14: Condyloma acuminatum - clinical manifestation¹¹.

The condyloma tends to be larger than the papilloma and is characteristically clustered with other condylomata. The average lesion size is 1.0 to 1.5 cm, but oral lesions as large as 3 cm have been reported.²⁵

DIFFERENTIAL DIAGNOSIS¹¹

Condyloma acuminatum may resemble focal epithelial hyperplasia in some cases. Multiple intraoral warts (verruca vulgaris) may be a consideration and indeed represent the same type of infection. Although condylomas tend to show more parakeratosis and **acanthosis** than verruca **vulgaris**, there are no universally accepted microscopic features that can be used to reliably separate the two.

DIAGNOSIS¹¹

- Location and appearance
- Demonstration of koilocytotic cellular changes on biopsy
- In situ hybridization or polymerase chain reaction reveals specific HPV subtype
- Electron microscopy demonstrates intranuclear virions

HISTOPATHOLOGY¹

Condyloma acuminatum appears as a benign proliferation of acanthotic stratified squamous epithelium with mildly keratotic papillary surface projections (**Figure 15**).



Figure 15: Condyloma acuminatum appears as a benign proliferation of acanthotic stratified squamous epithelium with mildly keratotic papillary surface projections¹

Thin connective tissue cores support the papillary epithelial projections, which are more blunted and broader than those of squamous papilloma and verruca vulgaris, imparting an appearance of keratin-filled crypts between prominences. The covering epithelium is mature and differentiated, but the prickle cells often demonstrate pyknotic nuclei surrounded by clear zones (koilocytes), a microscopic feature of HPV infection (**Figure 15**).¹⁴

TREATMENT AND PROGNOSIS

The oral condyloma is usually treated by conservative surgical excision. Laser ablation also has been used, but this treatment has raised some question as to the airborne spread of HPV through the aerosolized micro-droplets created by the vaporization of lesional

tissue. Regardless of the method used, a condyloma should be removed because it is contagious and can spread to other oral surfaces and to other persons through direct (usually sexual) contact.¹⁴

WARTY DYSKERATOMA

INTRODUCTION:

The warty dyskeratoma is a distinctly uncommon solitary lesion that can occur on skin or oral mucosa. It is histopathologically identical to Darier's disease. For this reason, the lesion has been termed isolated Darier's disease. The lesion is not otherwise related to Darier's disease, however, and its cause remains unknown.^{26,27}

CLINICAL FEATURES

It typically appears as a solitary, asymptomatic, umbilicated papule on the skin of the head or neck of an older adult. The intraoral lesion also develops in patients older than age 40, and a slight male predilection has been identified. The intraoral warty dyskeratoma appears as a pink or white, umbilicated papule located on the keratinized mucosa, especially the hard palate and the alveolar ridge. A warty or roughened surface is noted in some lesions. Most warty dyskeratomas are smaller than 0.5 cm in diameter.¹⁴

HISTOPATHOLOGY

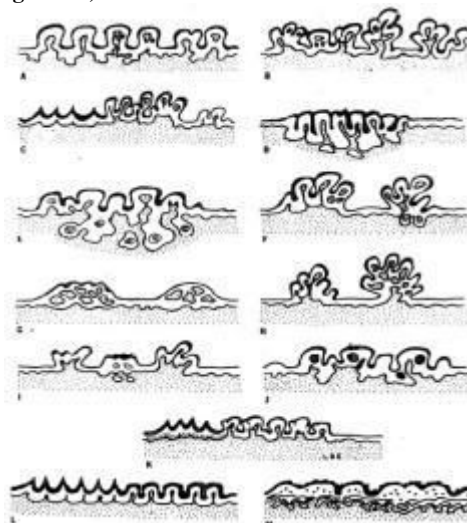
It appears very similar to keratosis follicularis. Both conditions display dyskeratosis and a suprabasilar cleft. It is a solitary lesion, however, and the formation of *corps, ronds* and grains is not a prominent feature.¹⁴

TREATMENT AND PROGNOSIS¹⁴

Treatment of the warty dyskeratoma consists of conservative excision. The prognosis is excellent; these lesions have not been reported to recur, and they have no apparent malignant potential. Careful histopathologic evaluation of the tissue should be performed because some epithelial dysplasias may show a marked lack of cellular cohesiveness, resulting in a similar acantholytic appearance microscopically.

MULTIFOCAL PAPILLARY LESIONS

Multifocal papillary and verrucous lesions of the oral mucosa are characterized by multiple lesions with intervening zones of normal appearing mucosa. Diffuse papillary lesions may be localized to a given site or fields yet are extensive and may, for example, cover the entire palate or extend across the entire mucobuccal fold in the quadrant. Multiple polypoid lesions represent large papules or nodules and may or may not be distributed over zones of normal appearing mucosa (**Figure 16**).



The disease entities manifesting these clinical signs are represented by neoplastic, reactive and genetic processes, some of which are associated with dermal or enteric concomitant inflammatory or neoplastic processes thereby representing oral mucosal markers of internal illness. The diseases included in this group are enumerated as follow.

- Papillary Hyperplasia (Figure 16A)
- Florid Papillomatosis (Figure 16B)
- Nevis Unis Lateris (Figure 16C)
- Verrucous Carcinoma (Figure 16D)
- Papillary Exophytic Squamous Cell Carcinoma (Figure 16E)
- Multiple Condylomata (Figure 16F)
- Focal Epithelial Hyperplasia (Figure 16G)
- Focal Dermal Hypoplasia Syndrome (Figure 16H)
- Multiple Hamartoma Syndrome (Figure 16I)
- Pyostomatitis Vegetans (Figure 16J)
- Acanthosis Nigricans (Figure 16K)
- Verruciform Leukoplakia (Figure 16L)
- Keratosis Follicularis (Figure 16M)

PAPILLARY INFLAMMATORY HYPERPLASIA

CLINICAL FEATURES:

The lesional tissue may be pink or erythematous and is confined to the palatal vault without extension onto the alveolar crest (**Figure 17**).



Figure 17: Denture inflammatory papillary hyperplasia (papillomatosis)²⁸

The lesions evolve in response to irritation from an ill-fitting denture which usually fails to exhibit direct contact with the tissue thereby creating negative pressure²⁸. (**O'Driscoll 1965**) The individual polyps are easily separated with a dental explorer¹. (**Eversol, 2000**) They are

not hyperkeratotic, and for this reason their coloration is that of normal mucosa. The lesion is often secondarily infected with *Candida* microorganisms. The lesion is not precancerous. It may be noted in habitual mouth breathers (nondenture wearers)¹⁴.

DIFFERENTIAL DIAGNOSIS

The range of possibilities in the differential diagnosis of papillary hyperplasia of hard palate is rather narrow because this particular entity is seldom confused with other forms of pathology. The chief lesion to be separated from papillary hyperplasia is nicotine stomatitis involving the hard palate; however, nicotine stomatitis does not occur on the, hard palate of those who wear complete maxillary removable appliances. Also, nicotine stomatitis tends to be more keratinized and usually demonstrates the presence of a small red dot or punctum in the center of each nodular excrescence, which represents the orifice of the subjacent minor salivary gland duct. Rarely, in **Darier's disease**, the mucosa of the palate may demonstrate numerous papules. Numerous squamous papillomas may occur on the palate; however, these lesions tend to be more keratinized with more delicate projections¹⁴.

In the so-called malignant form of **acanthosis nigricans**, oral lesions are papillary in nature and may regress relative to the treatment response of the underlying distant malignancy. Finally, in the multiple hamartoma syndrome (**Cowden's, syndrome**) the oral mucosa may exhibit numerous papillary mucosal nodules. These nodules, composed of benign fibro epithelial proliferations, may impart a cobblestone appearance, but usually to the tongue, buccal mucosa, and gingiva.

DIAGNOSIS¹

- Clinical appearance
- Biopsy results show fibrous and epithelial papillary hyperplasia; may note pseudoepitheliomatous hyperplasia

HISTOPATHOLOGY¹⁴:

Histologically multiple rounded polypoid excrescences are observed with a parakeratin layer of variable thickness. Submucosal papillae support these dome-shaped epithelial polyps and the base shows acanthosis with pseudoepitheliomatous hyperplasia. A diffuse mononuclear inflammatory infiltrate lies in juxtaposition to the papillary epithelial layer with transmigration into the lower spinous layer (i.e. epidermitis, chronic) (**Figure 18**).

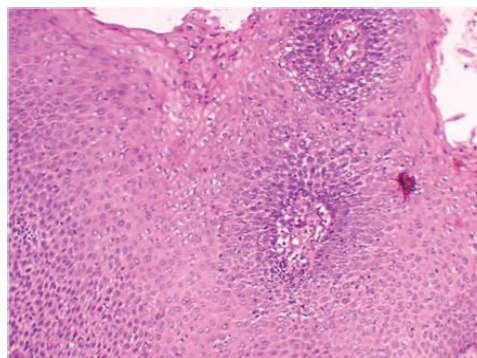
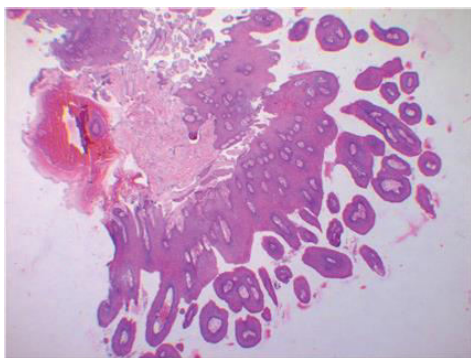


Figure 18: (a) Photomicrograph of the lesion showing multiple papillary epithelial projections with fibrovascular connective tissue cores (H&E, 4x). (b) Lesion showing koilocytes (arrows) in the epithelium. Koilocytes display a hyperchromatic shrunken nucleus with clear cytoplasm (perinuclear halo)²⁸ (H&E, 10x).

TREATMENT AND PROGNOSIS¹⁶:

Surgical removal is indicated before a denture is reconstructed for the patient. The actual surgical method is often a matter of individual preference and may include curettage, cryosurgery, electrosurgery, mucoabrasion, or laser ablation. Removal of appliances at bedtime and soaking in a weak disinfecting or antifungal medium, as well as maintenance of good oral hygiene coupled with topical antifungal therapy, may significantly reduce the intensity of lesions. In mild cases the use of soft tissue conditioning agents and liners, with frequent changing of the lining material, can produce sufficient resolution to preclude surgery. Topical antifungal ointment, either alone or mixed with a corticosteroid ointment, may also help reduce the size and intensity of the lesions. (Neville *et al.*, 2005)

ORAL FLORID PAPILOMATOSIS

This is an extremely rare disorder. Florid papillomatosis can involve both oral and laryngeal mucosa. It appears as a cobblestone diffuse lesion with superimposed pedunculated papillomas which may diffusely involve the entire oral cavity. Very little information is available on this entity. Now a day it is said that both proliferative verrucous leukoplakia and verrucous carcinoma may have been reported in the past by the name of florid papillomatosis.¹⁴ Oral florid papillomatosis' is synonymous with verrucous carcinoma and is a term which **can safely be discarded** and consigned to history.⁵ Microscopically the epithelium shows multiple confluent polypoid projections with foci of pedunculated papillomas evincing rounded blunt projections. The parakeratin layer is thickened as is the spinous layer and hyperplastic anastomosing rete ridges are present. A chronic inflammatory infiltrate occupies the immediate subjacent fibrous connective tissue. Treatment is enigmatic due to the extent of the lesions. Podophyllum resin is not effective. Staged surgical stripping, electro cautery or cryosurgery is recommended.²⁹

VERRUCOUS CARCINOMA

Snuff Dipper's Cancer; Ackerman's Tumor³²

Verrucous carcinoma is a low-grade variant of oral squamous cell carcinoma. Reported first by **Ackerman** in 1948 as a spit tobacco-associated malignancy, it has been diagnosed since then at several extraoral sites, including laryngeal, vaginal, and rectal mucosa, and skin from the breast, axilla, ear canal, and soles of the feet. (Ackerman, 1948) Tumors at anatomic sites other than the mouth are unrelated to tobacco use. Several investigators have identified HPV subtypes 16 and 18 in some oral verrucous carcinomas, but the significance of this is unclear³². Verrucous carcinoma represents 1% to 10% of all oral squamous cell carcinomas, depending on the local popularity of spit tobacco use. Many verrucous carcinomas arise from the oral mucosa in people who chronically use chewing tobacco or snuff, typically in the area where the tobacco is habitually placed. Cases also may occur in nonusers, but the exact figure is difficult to assess because patients will often deny the tobacco habit. In spit tobacco users, a regular squamous cell carcinoma is 25 times more likely to develop than this low-grade variant¹⁴. (Neville *et al.*, 2005)

CLINICAL FEATURES³³

Verrucous carcinoma is found predominantly in men older than 55 years of age (average age, 65 to 70 years). In areas where women are frequent users of spit tobacco, however, elderly females may predominate. The most common sites of oral mucosal involvement include the mandibular vestibule, the buccal mucosa, and the hard palate. The site of occurrence often corresponds to the site of chronic tobacco placement. In cultural groups who keep spit tobacco in the maxillary vestibule or under the tongue, these locations are the most commonly involved sites. Oral verrucous carcinoma is usually

extensive by the time of diagnosis, and it is not unusual for a tumor to be present in the mouth for 2 to 3 years before definitive diagnosis. The lesion appears as a diffuse, well-demarcated, painless, thick plaque with papillary or verruciform surface projections (**Figure 19**).



Figure 19: Clinical manifestation of Verrucous carcinoma¹⁴

Lesions are typically white but also may appear erythematous or pink. The color depends on the amount of keratin produced and the degree of host inflammatory response to the tumor. Leukoplakia or tobacco pouch keratosis may be seen on adjacent mucosal surfaces, and verrucous carcinoma is a lesion that may develop from the high-risk precancer, proliferative verrucous leukoplakia (PVL). Both PVL and verrucous carcinoma may have been reported in the past by the name oral florid Papillomatosis.¹⁴

DIFFERENTIAL DIAGNOSIS³³

1. Conventional squamous cell carcinoma
2. Leukoplakia; proliferative verrucous leukoplakia (PVL)
3. Traumatic lesion, factitial (self-induced) injury
4. Smokeless tobacco keratosis
5. Squamous papilloma, verruca vulgaris
6. Verrucous hyperplasia

In well-developed cases of verrucous carcinoma, the clinical pathologic diagnosis is relatively straightforward. However, in less than obvious 50 situations, leukoplakia might be a clinical consideration. A differential diagnosis would also include papillary squamous carcinoma, which may be distinguished from verrucous carcinoma by its more infiltrative nature, its greater degree of cytological atypia, and its more rapid growth. Verrucous carcinoma may develop from preexisting (and usually multiple) leukoplakia, representing part of the spectrum of proliferative verrucous leukoplakia.

HISTOPATHOLOGY

Verrucous carcinoma (VC) has a deceptively benign microscopic appearance. It is characterized by wide and elongated rete ridges that appear to "push" into the underlying connective tissue (**Figure 20**). VC invades the stroma with a pushing, rather than infiltrating border. Dense lymphoplasmacytic host response is common. Intraepithelial microabscesses are seen, and the abundant keratin may evoke a foreign body reaction¹⁴.

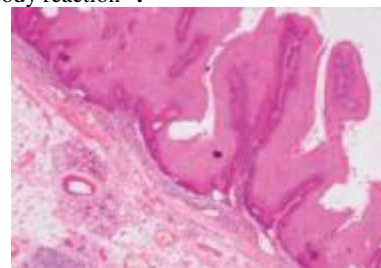


Figure 20: H & E x100, section shows bulbous proliferation of edges, acanthosis, and hyperkeratosis.

A downward dipping of epithelium often “cups” the VC periphery, and is the ideal site for deep biopsy.³⁵ Lesions usually show abundant keratin (usually parakeratin) production and a papillary or verruciform surface. Parakeratin typically fills the numerous clefts or crypts (**parakeratin plugs**) between the surface projections. These projections may be long and pointed or short and blunted. The lesional epithelial cells generally show a normal maturation pattern with no significant degree of cellular atypia (**Figure 20**)¹⁴. There is frequently an intense infiltrate of chronic inflammatory cells in the subjacent connective tissue. The histopathologic diagnosis of verrucous carcinoma requires an adequate incisional biopsy. Because the individual cells are not very dysplastic the pathologist must evaluate the overall histomorphologic configuration of the lesion to arrive at an appropriate diagnosis. Adequate sampling also is important because as many as 20% of these lesions have a routine squamous cell carcinoma developing concurrently within the verrucous carcinoma.³⁶

TREATMENT AND PROGNOSIS

Because metastasis is an extremely rare event in verrucous carcinoma, the treatment of choice is **extensive surgical excision without radical neckdissection**. The surgery generally need not be as extensive as that required for routine squamous cell carcinoma of a similar size. With this treatment, 90% of patients are disease free after 5 years, although some patients will require at least one additional surgical procedure during that time. The treatment failures usually occur in patients with the most extensive involvement or in those unable to tolerate extensive surgery because of unrelated systemic diseases. An additional cause of treatment failure is the initial inability to identify a focal squamous cell carcinoma arising concurrently within the less aggressive lesion¹⁴. Radiotherapy is effective, but has been less popular because of published reports of poorly differentiated or anaplastic carcinoma developing within the lesion after radiotherapy. A recent analysis suggests that this threat is seriously over exaggerated, and that similar dedifferentiation can occur in verrucous carcinomas treated surgically. Chemotherapy may temporarily reduce the size of verrucous carcinoma, but it is not considered a definitive, stand-alone treatment¹.

EXOPHYTIC PAPILLARY SQUAMOUS CELL CARCINOMA

Papillary squamous cell carcinoma (PSCC) is a distinct variant of SCC characterized by an exophytic, papillary growth, and a favorable prognosis.³⁶ This is rarely recognized in the oral cavity and oropharynx other than as a component of a large SCC. It is usually associated with the tumors of the hypopharynx, larynx and trachea. (Cardesa et al., 2005) Occasionally, invasive squamous cell carcinoma will present as a papillary or verrucous lesion mimicking verrucous carcinoma. An exophytic lesion typically has a surface that is irregular, fungating, papillary, or verruciform, and its color may vary from normal to red to white, depending on the amount of keratin and vascularity (Figures 21). The surface is often ulcerated, and the tumor feels hard (indurated) on palpation. Microscopically, a polypoid or papillary architecture is observed. In contradistinction to verrucous carcinoma, spinous layer keratinocytes display cytological atypia. Pearl formation is observed and an invasive pattern of growth is witnessed at the inferior margin. The neck should be palpated for nodal enlargement.¹⁴

TREATMENT

Treatment includes standard treatment for squamous cell carcinoma.³⁶



Figure 21: An exophytic lesion of the posterior lateral tongue demonstrates surface nodularity and minimal surface keratin production

MULTIPLE CONDYLOMATA

The clinical and microscopic features for condyloma acuminatum have been detailed under focal lesions. Suffice it to mention here that oral venereal warts frequently occur in groups and clusters separated from one another by intervening zones of normal appearing mucosa. Since the lesion is virally transmitted, seeding can occur with development of multiple adjacent lesions.³⁷

Focal Epithelial Hyperplasia

Heck's Disease; Multifocal Papilloma Virus Epithelial Hyperplasia⁴⁰. Multiple oral papillomas induced by HPV 13 and 32³⁹.

Focal epithelial hyperplasia is a virus-induced, localized proliferation of oral squamous epithelium that was first described in Native Americans and Inuits (Eskimos)⁴¹. It is confined to oral mucosa (i.e., there are no genital or cutaneous foci of involvement). The lesions are more common in central and South America than in other areas, currently, it is known to exist in many populations and ethnic groups and is apparently produced by the human papillomavirus type 16 and possibly 18⁴². The frequency of this disease is variable with wide range from 0.002 to 35% depending on the population studied and geographic region⁴³.

CLINICAL FEATURES^{39, 40, 14}

Usually a **childhood condition**, focal epithelial hyperplasia occasionally affects young and middle-aged adults. There is no gender bias. Sites of greatest involvement include the labial, buccal, and lingual mucosa, but gingival and tonsillar lesions also have been reported. This disease typically appears as multiple soft, non-tender, flattened or rounded papules, which are usually clustered and the color of normal mucosa, although they may be scattered, pale, or rarely white (**Figure 22**).



Figure 22: Focal epithelial hyperplasia, multiple lip and tongue nodules³⁹.

Occasional lesions show a slight papillary surface change. Individual lesions are small (0.3 to 1.0 cm), discrete, and well demarcated, but they frequently cluster so closely together that the entire area takes on a cobblestone or fissured appearance. (Tan et al., 1995)

DIFFERENTIAL DIAGNOSIS¹⁴

A differential diagnosis would include verruca vulgaris and multiple squamous papillomas. The oral mucosal lesions of Cowden's (multiple hamartoma) syndrome may present similarly and should be ruled out. In addition, oral manifestations of Crohn's disease and Pyostomatitis Vegetans might be considered.

HISTOPATHOLOGY^{39, 40, 42}

The hallmark of focal epithelial hyperplasia is an abrupt and sometimes considerable acanthosis of the oral epithelium (Figure 23).

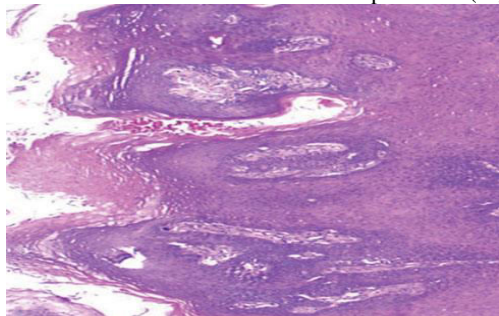


Figure 23: Squamous epithelium with parakeratosis, acanthosis and marked papillomatosis (x100)

Because the thickened mucosa extends upward, not down into underlying connective tissues, the lesion's rete ridges are at the same depth as the adjacent normal rete ridges. The ridges themselves are widened, often confluent, and sometimes club shaped. Some superficial keratinocytes show a koilocyte change similar to that seen in other HPV infections. Others occasionally demonstrate an altered nucleus that resembles a mitotic figure (**mitosoid cell**). Virus like particles have been noted ultra-structurally within both the cytoplasm and the nuclei of cells within the prickle cell layer, and the presence of HPV has been demonstrated with both DNA *in situ* hybridization and immunohistochemical analysis.

TREATMENT AND PROGNOSIS¹⁴

Spontaneous regression of focal epithelial hyperplasia has been reported after months or years and is inferred from the rarity of the disease in adults. Conservative surgical excision of lesions may be performed for diagnostic or aesthetic purposes. The risk of recurrence after this therapy is minimal, and there seems to be no malignant transformation potential.

FOCAL DERMAL HYPOPLASIA

Multiple defects are observed in focal dermal hypoplasia or the **Goltz Gorlin syndrome**. This hereditary disease is observed in children who present with putty-like pigmented nodular lesions of extremity skin in which the subcutaneous fat has herniated through defective dermal connective tissue. Oral and labial multifocal papillomas are observed appearing as pedunculated racemose clusters with intervening normal mucosa. These children often manifest mental retardation, iridal colobomas, syndactylism and strabismus.⁴⁴

Microscopically the papillary lesions are similar in appearance to focal squamous papilloma. The epithelial proliferations are blunt and rounded with a layer of parakeratin and a somewhat thickened spinous layer. Fibrous connective tissue fronds support the epithelial proliferations. Surgical excision, electro cautery or cryosurgery is the treatments of choice.⁴⁴

MULTIPLE HAMARTOMA SYNDROME

Cowden Syndrome⁴⁵

Multiple hamartoma syndrome is a rare condition that has important implications for the affected patient, because malignancies, in addition to the benign hamartomatous growths, develop in a high percentage of these individuals. This is a multisystem disease. Usually, the syndrome is inherited as an **autosomal dominant trait** showing a high degree of penetrance and a range of expressivity. The gene responsible for this disorder has been mapped to chromosome 10, and a mutation of the **PTEN (phosphatase and tensin homolog deleted on chromosome 10)** gene has been implicated in its pathogenesis. Over 170 affected patients have been described in the literature⁴⁵.

CLINICAL FEATURES^{14, 45}

Cutaneous manifestations are present in almost all, usually developing during the second decade of life. The majority of the skin lesions appear as multiple, small (less than 1 mm) papules, primarily on the facial skin, especially around the mouth, nose, and ears. Microscopically, most of these papules represent hair follicle hamartomas called trichilemmomas. Other commonly noted skin lesions are acral keratosis, a warty-appearing growth that develops on the dorsal surface of the hand, and palmoplantar keratosis, a prominent callus like lesion on the palms or soles. Cutaneous hemangiomas, xanthomas, and lipomas have also been described. Other problems can appear in these patients as well. Thyroid disease usually appears as either a goiter or a thyroid adenoma, but follicular adenocarcinoma may develop. In women, fibrocystic disease of the breast is frequently observed. Unfortunately, breast cancer occurs with a relatively high frequency (20% to 36%) in these patients. The mean age at diagnosis of breast malignancy is 40 years, which is much younger than usual. In the gastrointestinal tract, multiple benign hamartomatous polyps may be present. In addition, several types of benign and malignant tumors of the female genitourinary tract occur more often than in the normal population. The oral lesions vary in severity from patient to patient and usually consist of multiple papules affecting the gingiva, dorsal tongue, and buccal mucosa (Figures 24).



Figure 24: Multiple, irregular fibroepithelial papules involve the tongue (center) and alveolar ridge mucosa

These lesions have been reported in more than 80% of affected patients and generally produce no symptoms. Other possible oral findings include a high-arched palate, periodontitis, and extensive dental caries, although it is unclear whether the latter two conditions are significantly related to the syndrome. (Neville et al., 2005)

DIAGNOSIS¹⁴:

The diagnosis is based on the finding of two of the following three signs:

- Multiple facial trichilemmomas
- Multiple oral papules
- Acral keratoses

A positive family history is also helpful in confirming the diagnosis.

HISTOPATHOLOGY⁴⁵:

The histopathology of the oral lesions is rather **nonspecific**, essentially representing fibroepithelial hyperplasia. Other lesions associated with this syndrome have their own characteristic histopathologic findings, depending on the hamartomatous or neoplastic tissue origin.

TREATMENT AND PROGNOSIS^{14, 45}:

Treatment of multiple hamartoma syndrome is controversial. Although most of the tumors that develop are benign, the prevalence of malignancy is higher than in the general population. Some investigators recommend bilateral prophylactic mastectomies as early as the third decade of life for female patients because of the associated increased risk of breast cancer.

ACANTHOSIS NIGRICANS

Acanthosis nigricans is an acquired dermatologic problem characterized by the development of a velvety, brownish alteration of the skin. In some instances, this unusual condition develops in conjunction with gastrointestinal cancer and is termed malignant acanthosis nigricans⁴⁶. The cutaneous lesion itself is benign, yet it is significant because it represents a cutaneous marker for internal malignancy. The cause of malignant acanthosis nigricans is unknown, although a cytokine-like peptide capable of affecting the epidermal cells may be produced by the malignancy.¹⁴

Most cases, estimated to affect as many as 5% of adults, are not associated with a malignancy and are termed benign acanthosis nigricans. A clinically similar form, pseudoacanthosis nigricans, may occur in some obese people. Some benign forms of acanthosis nigricans may be inherited or may occur in association with various endocrinopathies, such as diabetes mellitus, Addison's disease, hypothyroidism, and acromegaly. Furthermore, benign acanthosis nigricans may occur with certain syndromes (e.g., Crouzon syndrome) or drug ingestion (oral contraceptives, corticosteroids). These forms of the condition are typically associated with resistance of their tissues to the effects of insulin, similar to the insulin resistance seen in noninsulin-dependent diabetes mellitus. Even though the affected individuals may not have overt diabetes mellitus, they often show increased levels of insulin or an abnormal response to exogenously administered insulin.⁴⁷

CLINICAL FEATURES^{14, 47}

The malignant form of acanthosis nigricans develops in association with an internal malignancy, particularly adenocarcinoma of the gastrointestinal tract. Approximately 20% of the cases of malignant acanthosis nigricans are identified before the malignancy is found, but most appear at about the same time as discovery of the gastrointestinal tumor or thereafter. Both forms of acanthosis nigricans affect the flexural areas of the skin predominantly, appearing as finely papillary, hyperkeratotic, brownish patches that are usually asymptomatic. The texture of the lesions has been variably described as either velvety or leathery.

Oral lesions of acanthosis nigricans have also been reported and may occur in 25% to 50% of affected patients, especially those with the malignant form. These lesions appear as diffuse, finely papillary areas of mucosal alteration that most often involve the tongue or lips, particularly the upper lip (**Figure 25**).



Figure 25: Diffuse verrucous papillomatous papules and plaques on the upper and lower vermilion

HISTOPATHOLOGY

The histopathology of the various forms of acanthosis nigricans is essentially identical. The epidermis exhibits hyperorthokeratosis and papillomatosis. Usually, some degree of increased melanin deposition is noted, but the extent of acanthosis (thickening of the spinous layer) is really rather mild. The oral lesions have much more acanthosis, but show minimal increased melanin pigmentation⁴⁷.

TREATMENT AND PROGNOSIS^{14, 47}

Although acanthosis nigricans itself is a harmless process, the patient should be evaluated to ascertain which form of the disease is present. Identification and treatment of the underlying malignancy obviously are important for patients with the malignant type; unfortunately, the prognosis for these individuals is very poor. Interestingly, malignant acanthosis nigricans may resolve when the cancer is treated. Keratolytic agents may improve the appearance of the benign forms.

VERRUCIFORM LEUKOPLAKIA

Leukokeratosis, Oral Proliferative Leukoplakia⁴⁸

Oral leukoplakia (*leuko* — white; *plakia* — patch) is defined by the World Health Organization (WHO) as "a white patch or plaque that cannot be characterized clinically or pathologically as any other disease." The term is strictly a clinical one and does not imply a specific histopathologic tissue alteration¹⁴. (Neville *et al.*, 2005)

CLINICAL FEATURES

Leukoplakia usually affects persons older than 40 years of age. Prevalence increases rapidly with age, especially for males, and as many as 8% of men older than 70 years of age reportedly are affected. The average age of affected persons (60 years) is similar to the average age for patients with oral cancer; however, in some studies leukoplakia has been found to occur about 5 years earlier (on average) than oral squamous cell carcinoma⁴⁸.

Individual lesions may have a varied clinical appearance and tend to change over time. Early and mild lesions appear as slightly elevated gray or graywhite plaques, which may appear somewhat translucent, fissured, or wrinkled and are typically soft and flat (**Figure 26**)¹⁴.



Figure 26: Exophytic papillary lesion of the anterior maxillary alveolar ridge¹⁴

They usually have sharply demarcated borders but occasionally blend gradually into normal mucosa. **Mild** or **thin leukoplakia**, which seldom shows dysplasia on biopsy, may disappear or continue unchanged. For tobacco smokers who do not reduce their habit, as many as two thirds of such lesions slowly extend laterally, become thicker, and acquire a distinctly white appearance. The affected mucosa may become leathery to palpation, and fissures may deepen and become more numerous. At this stage or phase, the lesion is often called a **homogeneous** or **thick leukoplakia**. Most thick, smooth lesions remain indefinitely at this stage. Some, perhaps as many as one third, regress or disappear; a few become even more severe, develop increased surface irregularities, and are then called **granular** or **nodular leukoplakia**. Some lesions demonstrate sharp or blunt projections and have been called **verrucous** or **verruciform leukoplakia**.¹⁴

HISTOPATHOLOGY¹⁴

Microscopically, leukoplakia is characterized by a thickened keratin layer of the surface epithelium (hyperkeratosis), with or without a thickened spinous layer (acanthosis). Some leukoplakias demonstrate surface hyperkeratosis but show atrophy or thinning of the underlying epithelium. Frequently, variable numbers of chronic inflammatory cells are noted within the subjacent connective tissue. The keratin layer may consist of parakeratin (hyper-parakeratosis), orthokeratin (hyperorthokeratosis), or a combination of both (**Figure 27**) with parakeratin, there is no granular cell layer and the epithelial nuclei are retained in the keratin layer. With orthokeratin, the epithelium demonstrates a granular cell layer and the nuclei are lost in the keratin layer.

Verrucous leukoplakia has papillary or pointed surface projections, varying keratin thickness, and broad, blunted rete ridges. It may be difficult to differentiate it from early verrucous carcinoma.⁴⁹

TREATMENT AND PROGNOSIS

Because leukoplakia represents a clinical term only, the first step in treatment is to arrive at a definitive histopathologic diagnosis. Therefore, a biopsy is mandatory and will guide the course of treatment. Tissue obtained for biopsy, moreover, should be taken from the clinically most "severe" areas of involvement.¹⁴ Multiple biopsies

of large or multiple lesions may be required. Leukoplakia exhibiting moderate epithelial dysplasia or worse warrants complete destruction or removal, if feasible. The management of leukoplakia exhibiting less severe change is guided by the size of the lesion and the response to more conservative measures, such as smoking cessation. Complete removal can be accomplished with equal effectiveness by surgical excision, electrocautery, cryosurgery, or laser ablation. Long-term follow-up after removal is extremely important because recurrences are frequent and because additional leukoplakias may develop. This is especially true for the verruciform or granular types, 83% of which recur and require additional removal or destruction¹⁴.

DARIER'S DISEASE

Keratosis Follicularis; Dyskeratosis Folucularis; Darier-WhiteDisease⁵¹

Darier's disease is an uncommon genodermatosis with rather striking skin involvement and relatively subtle oral mucosal lesions. The condition is inherited as an **autosomal dominant trait**, having a high degree of penetrance and variable expressivity.⁵² A lack of cohesion among the surface epithelial cells characterizes this disease, and mutation of a gene that encodes an intracellular calcium pump has been identified as the cause for abnormal desmosomal organization in the affected epithelial cells. Estimation of the *prevalence of Darier's disease* in northern European populations range from 1 in 36,000 to 1 in 100,000.⁵³

CLINICAL FEATURES:

Patients with Darier's disease have numerous erythematous, often pruritic, papules on the skin of the trunk and the scalp that develop during the second decade of life. An accumulation of keratin, producing a rough texture, may be seen in association with the lesions, and a foul odor may be present as a result of bacterial degradation of the keratin. The process generally becomes worse during the summer months, either because of sensitivity of some patients to ultraviolet light or because increased heat results in sweating, which induces more epithelial clefting. The palms and soles often exhibit pits and keratoses.^{53, 54} The nails show longitudinal lines, ridges, or painful splits.

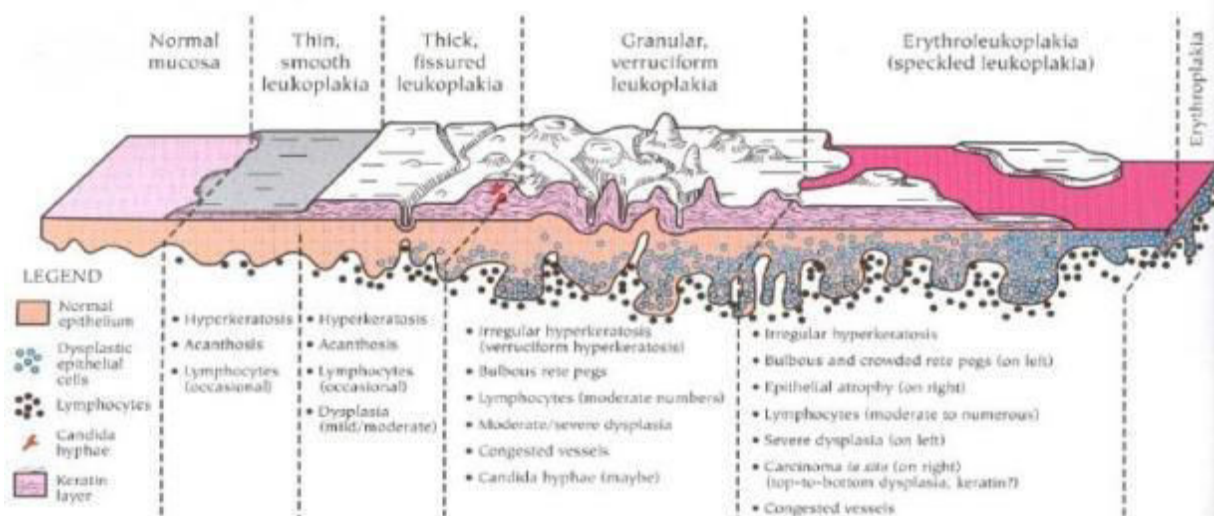


Figure 27: Composite representation of the various phases or clinical appearances of oral leukoplakia, with anticipated underlying histopathologic changes. Lesions have increasing malignant transformation potentials as their appearances approach those toward the right¹⁴.

The oral lesions are typically asymptomatic and are discovered on routine examination. The frequency of occurrence of oral lesions ranges from 15% to 50%. They consist of multiple, normal-colored or white, flat-topped papules that, if numerous enough to be confluent, result in a cobblestone mucosal appearance (**Figure 28**).⁵⁴



Figure 28: The oral mucosa may show multiple white papules⁵⁴

These lesions affect the hard palate and alveolar mucosa primarily, although the buccal mucosa or tongue may be occasionally involved. If the palatal lesions are prominent, the condition may resemble inflammatory papillary hyperplasia or nicotine stomatitis. Some patients with this condition also experience recurrent obstructive parotid swelling secondary to duct abnormalities.⁵³

HISTOPATHOLOGY^{14, 54}

Microscopic examination of the cutaneous or mucosal lesions shows a dyskeratotic process characterized by a central keratin plug that overlies epithelium exhibiting a suprabasilar cleft (**Figure 29**).

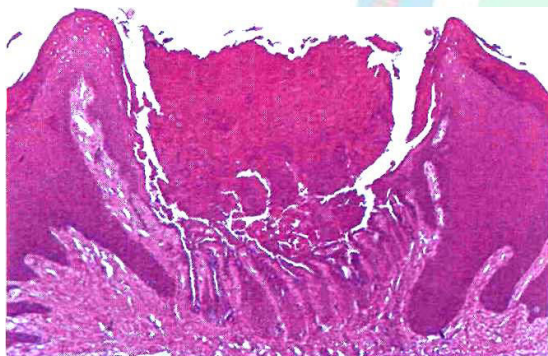


Figure 29: Darier's disease. Low-power photomicrograph showing a thick keratin plug, intraepithelial clefting, and elongated rete ridges⁵⁴

This intraepithelial clefting phenomenon, also known as **acantholysis**, is not unique to Darier's disease and may be seen in conditions such as pemphigus vulgaris. In addition, the epithelial rete ridges associated with the lesions appear narrow, elongated, and "test tube" shaped. Closer inspection of the epithelium reveals varying numbers of two types of dyskeratotic cells, called corps, **ronds** (round bodies) or grains (because they resemble cereal grains).

TREATMENT AND PROGNOSIS⁵³

Treatment of Darier's disease depends on the severity of involvement. Photosensitive patients should use a sunscreen, and all patients should minimize unnecessary exposure to hot environments. For relatively mild cases, **keratolytic** agents may be the only treatment required. For more severely affected patients, systemic **retinoids** are often beneficial, but the side effects of such medications have to be carefully monitored by the physician.

Although the condition is not premalignant or otherwise life threatening, genetic counseling is appropriate.¹⁴ (**Neville et al., 2005**)

CONCLUSION:

In all instances microscopic examination is essential and must be coordinated with the clinical findings in order to allow for a definitive diagnosis.

REFERENCES:

1. Eversol LR. Human Papillomaviruses and papillary oral Lesions. 2000:144-51
2. H Singh, P Kumar, A Kumar. Possible role of Human Papilloma Virus in Oral Disease- An Update. The International Journal of Infectious Diseases 2010; 9(2): 1-6.
3. Costa LJ, Da Silveira FR, Batista JM, Birman EG. Human Papilloma Virus- Its Association with Epithelial Proliferative Lesions. Braz Dent J 1994; 5(1): 5-10
4. Kestenbaum TM. "Textbook of Dermatology" 1987: 137
5. Thomas GJ, Barrett AW. Papillary and Verrucous Lesions of the oral mucosa. Diagnostic Histopathology 2009; 15(6): 279-85.
6. Textbook of a Guide to Common Oral Lesions by Dr. Charles L. Dunlap, Dr. Bruce F. Barker. 3
7. Thomas C, Wright, Jr. Pathology of HPV infection at the cytologic and histologic levels: Basis for a 2-tiered morphologic classification system. International Journal of Gynecology and Obstetrics 2006; 94(1): S22-31.
8. Munoz N, Castellsague X, Gonzalez AB, Gissmann L. HPV in the etiology of human cancer. Journal of Vaccine 2006; 115(5): S31-10.
9. Abreu AL, Souza RP, Gimenes F, Consolaro ME. A Review of Methods for detect human Papillomavirus infection. Virology Journal 2012; 262(9): 1-9.
10. Sabarad P, Koppad S. The Role of Human Papilloma virus in Oral Lesions: A Review. Journal of Medical Science and Clinical Research 2015; 6(3): 6014-24.
11. Verrucal-Papillary Lesions. Textbook of Oral Pathology. PDQ Oral Disease: 140-59.
12. Singh AP, Jain S, Chaitra TR, Kulkarni AU. Oral squamous papilloma: report of a clinical rarity. BMJ Case Reports 2013.
13. Barroso dos Reis HL, et al. Recurrent Oral Squamous Papilloma in a HIV Infected Patient: Case Report.
14. Neville, Damn, Allen, Bouquot. Textbook of Oral and Maxillofacial Pathology. 3rd Edition.
15. Harrist TJ, Murphy GF, Mihm Mc. Oral Warty Dyskeratoma. Arch Dermatol 1980; 116: 929-30.
16. Joshi M, Shah A, Vishnoi S. Oral Verruca Vulgaris: Report of Two Rare Cases and Review. NJIRM 2013; 4(4): 145-48.
17. Basak S, Rajukar M. MolluscumContagiosum- An Update. Indian Medical Gazette 2013; 276-78.
18. MolluscumContagiosum. Information for patients, parents and carers. 2016.
19. Chandwani R et al. A rare case of VerruciformXanthoma. International Journal of Medical Sciences and Technology 2010; 3(1):5-8.
20. Shetty A, Nakhaei K, Lakkashetty M, Mohebatzadeh I. Oral VerruciformXanthoma: A Case Report and Literature Review. Case Reports in Dentistry 2013; (2013):1-4.
21. Byun JH, Kim DC, Go GH, Park BW. Sialadenomacpapilliferum: a case report and immunohistochemical study review. Journal of Korean Association Oral Maxillofacial Surgery 2010; 36: 533-7.

22. Pereira CM, Sousa HO, Gasparetto PF, Boltelho TL. Sialadenomapapilliferum: case report and review of literature. *Journal of Health Science Inst.* 2010; 28(3): 244-5.
23. Chaiben CL, Bohn JC, Kuczynski A, Dias Gil FB, Lima AA. Keratoacanthoma in the inferior lip of an immunosuppressed patient. A case report. *Stomatologija, Baltic Dental and Maxillofacial Journal* 2013; 2(15): 61-4.
24. Chen YK, Lin LM, Lin CC, Chen C. Keratoacanthoma of the tongue: A diagnostic problem. *American Academy of Otolaryngology- Head and Neck Surgery Foundation* 2003; (128): 581-2.
25. Kui LL, Xiu HZ, Ning LY. CondylomaAcuminatum and Human Papilloma Virus Infection in the Oral Mucosa of Children. *Journal of Pediatric Dentistry* 2003; 2(25): 149-53.
26. Janardhanan M, Vidya M. Association of Human Papilloma Virus with Oral Squamous Cell Carcinoma- A Brief Review. *Oral & Maxillofacial Pathology Journal* 2010; 2(1): 1-9.
27. Jang EJ, Lee JY, Kim MK, Yoon TY. Warty Dyskeratoma Involving Two Adjoining Follicles. *Ann Dermatol* 2011; 1(23): 98-100.
28. Al-osman A, Perry JB, Birek C. Extensive Papillomatosis of the Palate Exhibiting Epithelial Dysplasia and HPV 16 Gene Expression in a Renal Transplant Recipient. *Journal of Canadian Dental Association* 2006; 4(72): 331-34.
29. Grinspan D, Abulafia J. Oral Florid Papillomatosis(Verrucous Carcinoma). *International Society of Tropical Dermatology* 1979; (1000): 0608-24.
30. Regezi JA, Sciubba JJ. *Textbook of Oral Pathology- Clinical Pathologic Correlations.* 3rd Edition. 43-48.
31. Kannawat N, Kapmpirapap K. Systemic epidermal nevus and Nevus uniuslateralis: case reports. *Thai Journal of Dermatology* 2010; (26): 168-73.
32. Venkatesh M, Geetha P, Kumar BP, Namratha, Sunitha. Verrucous Carcinoma in the Oral Cavity- Report of two cases. *Indian Journal of Dental Advancements* 2012; 4(2): 859-62.
33. Warshaw EM, Stephan F, Washington CV. Verrucous Carcinoma Occurring in a Lesion of Oral Lichen Planus. 2000; (65): 219-22.
34. Neville BW, Damm DD, Allen CM, Bouquot JE (2005) "Epithelial Pathology. In: *Oral & Maxillofacial Pathology*", 2nd edition, New delhi, Saunders.
35. Devaney KO, Ferlito A, Rinaldo A, El-Naggar AK, Barnes L. Verrucous carcinoma (Carcinomacuniculatum) of the head and neck: what do we know now that we did not know a decade ago? *European Archives Otorhinolaryngology* 2011; 268: 477-80.
36. Odar K et al. Verrucous carcinoma of the head and neck- not a human papillomavirus-related tumour? *Journal of Cellular and Molecular Medicine published by John Wiley & Sons Ltd and Foundation for Cellular and Molecular Medicine* 2014; 4(18): 635-45.
37. CondylomaAcuminata. Maryland family planning & Reproductive Health Program Clinical Guidelines 2012; 1-2.
38. Beaudenon S, Praetorius F. A new type of Human Papillomavirus associated with oral focal Epithelial Hyperplasia. *The Society for Investigative Dermatology* 1987; 2(88): 130-35.
39. Durso BC, Pinto JV, Jorge J, Almeida OP. Extensive Focal Epithelial Hyperplasia: Case Report. *Journal of Canadian Dental Association* 2005; 71(10): 769-71.
40. Focal Epithelial Hyperplasia Heck's disease.
41. Puriene A, Rimkevicius A, Gaigalas M. Focal epithelial hyperplasia: Case report. *Stomatologija, Baltic Dental and Maxillofacial Journal* 2011; 13(3): 102-4.
42. Prabhat MP, Raja Lakshmi C, Madhavi N, Bhavana S, Sarat G, Ramamohan K. Multifocal Epithelial Hyperplasia of oral cavity Expressing HPV 16 Gene: A Rare Entity. *Case Reports in Dentistry* 2013; (2013): 1-4.
43. Hashemipour MA, Shoryabi A, Adhami S, Honarmand HM. Extensive Focal Epithelial Hyperplasia. *Archives of Iranian Medicine* 2010; 13(1): 48-52.
44. Ureles SD, Needleman HL. Focal dermal hypoplasia syndrome (Goltz syndrome): the first dental case report. *The American Academy of Pediatric Dentistry* 1986; 3(8): 239-44.
45. Goulas SS et al. Cowden's disease: A case report and review of the literature. *Annals of Gastroenterology* 2003; 16(1): 70-73.
46. Pentenero M, Carozzo M, Pagano M, Gandolfo S. Oral acanthosisnigricans, tripe palms and sign of leser-trelate in a patient with gastric adenocarcinoma. *International Journal of Dermatology* 2004; (43): 530-32.
47. Mcginness J, Greer K. Malignant AcanthosisNigricans and Triple Palms Associated With Pancreatic Adenocarcinoma. *Cutis* 2006; (78): 37-40.
48. Issrani R, Prabhu N, Keluskar V. Oral proliferative verrucous leukoplakia: A case report with an update. *Journal of Contemporary Clinical Dentistry* 2013; 2(4): 258-62.
49. Cheong ML. Hereditary mucosal leukokeratosis. *The International Society of Dermatology* 2009; (10): 1-3.
50. Shakil M, Mohtesham I, Jode M, Prabhu V. Carcinoma Cuniculatum of the Oral Cavity- A Rare Entity. *Journal of Advanced Medical and Dental Sciences Research* 2014; 2(1): 124-26.
51. Buteica E, Burada F, Stoicescu I, Stanoiu B, Georgescu V. Darier disease and Hailey-Hailey disease. *Romanian Journal of Morphology and Embryology* 2007; 48(4): 423-26.
52. Chung J et al. A Case of Familial comedonal Darier's Disease. *Annal of Dermatology* 2011; 23(3): S398-401.
53. Godic A. Darier disease. A review of pathophysiological mechanisms. *ActaDermatovenerologica* 2003; 12(4): 119-26.
54. Cardoso C, Freitas P, AssisTaveira LA, Consolaro A. Darier disease: case report with oral manifestations. *Journal of Oral Medicine and Pathology* 2006; 11: E404-6.
55. Schneller C, Finkel L, Wise M, Hageman JR, Littlejohn E. Autoimmune Polyendocrine Syndrome: A Case-Based Review. *Journal of Pediatric Annals* 2013; 42(5): 203-8.
56. Yamagata K, Bukawa H. *Textbook of Amyloidosis – An Insight to Disease of Systems and Novel Therapies.* 141-52.
57. Cengiz MI, Wang HL, Yildiz L. Oral involvement in a case of AA amyloidosis: a case report. *Journal of Medical case Reports* 2010; 4: 1-6.
58. Vasconcelos MG. Oral Lymphangioma: case report. *Journal of RevistaSul-Brasileira de Odontologia* 2010; 8(3): 352-6.
59. Sunil S, Gopalkumar D, Sreenivasan BS. Oral lymphangioma- Case reports and review of literature. *Journal of Contemporary Clinical Dentistry* 2012; 1(3): 116-8.

Source of support: Nil

Conflict of interest: None declared

This work is licensed under CC BY: *Creative Commons Attribution 3.0 License.*