Oral Verruciform Xanthoma: A Series of 212 Cases and Review of the Literature

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Abstract

Verruciform xanthoma (VX) of the oral cavity is an uncommon, reactive lesion of unknown etiology. In this study, we present a large series of VX with analysis of demographics, clinical appearance, histologic presentation and extensive review of literature. To the best of our knowledge, this is the largest series of oral VX reported to date. Following IRB approval, all cases diagnosed as VX found in the archives of the University of Florida Oral Pathology Biopsy Service (1994–2018) were included. Patient age, gender, location, clinical appearance, clinical impression, and duration of each lesion was collected. A total of 212 cases were included in our database with a mean age of 61 years (range of 9–94), and a female: male ratio of 1.06:1. The most common location in descending order was the gingiva (n = 110, 51.2%), followed by palate (n = 41, 19.3%), buccal mucosa (n = 18, 8.5%), tongue (n = 20, 9.4%), vestibule (n = 13, 6.1%), lip (n = 4, 1.9%), floor of mouth (n = 3, 1.4%), and unspecified (n = 1, 0.5%). The lesions were most frequently pink in color, and most often described as bumpy, rough, verrucoid and/or papillary. Clinical impression in descending order was papillary (n = 67, 31.6%), not specified or unknown (n = 41, 19.3%), hyperkeratosis (n = 24, 11.3%), fibroma (n = 20, 9.4%), leukoplakia (n = 17, 8.0%), dysplastic lesion (n = 13, 6.1%), pyogenic granuloma (n = 7, 3.3%), granulomatous reaction (n = 5, 2.4%), lichen planus, VX (n = 4 each, 2.0%), pigmented, other lesions (n = 3 each, 1.4%), and salivary and periapical lesions (n = 2 each, 0.9%). Three of the lesions were recurrences. The demographics and clinical parameters of this case series were in concordance with that of previously published reports. In our series, only 4 cases were suspected as VX, demonstrating the lack of familiarity clinicians have with this lesion.

Keywords Verruciform xanthoma · Oral verruciform xanthoma · Oral mucosa · Oral cavity · Benign papillary lesions · Epithelial pathology · Histology

Introduction

Verruciform xanthoma (VX) of the oral cavity is an uncommon, reactive lesion that was first described in 1971 by Shafer [1]. Rare extraoral VX, which occur on the skin and anogenital mucosa, have also been reported [2–6]. Buchner et al. reported an incidence rate of 0.025–0.095% for

oral VX within a 12 year period [7]. The etiology of oral VX remains unknown, however, proposed initiators include inflammation, trauma, and an altered immunological response, which releases lipid material [8]. Oral VX appear as asymptomatic, slow-growing, well demarcated plaques or nodules with a papillary or verrucous surface. The lesions can range in color from pink, red, white, or yellow. The majority of cases have been reported on masticatory mucosa including the attached gingiva and hard palate [9]. Oral VX lesions appear most commonly during the fifth and sixth decades of life, with a reported age range of 2–89 years old [10]. Due to the variable presentation, VX are frequently misdiagnosed clinically and are consistently diagnosed by microscopic examination.

Microscopically, the characteristic histologic finding in VX is the distinct accumulation of foamy macrophages within the elongated connective tissue papillae, between

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the acanthotic squamous epithelial ridges of uniform depth [11]. These lipid-laden foamy macrophages, commonly known as *xanthoma cells*, are believed to be a response to trauma or chronic inflammation. These histopathological features may mimic pseudoepitheliomatous hyperplasia and can possibly be confused with other entities microscopically [12]. More commonly, this rare lesion also may be clinically confused with potentially malignant lesions. The purpose of this article is to present a large case series of oral VX and review the literature with regard to demographics, clinical appearance, and histologic presentation. To the best of our knowledge this is the largest case series of oral VX in the literature.

Material and Methods

With IRB approval, the archives of the University of Florida Oral Pathology Biopsy Service were searched for verruciform xanthoma cases arising in the oral cavity between the years of 1994–2018. The following parameters for each case were tabulated which included the age, sex, location of each lesion, duration, clinical appearance, clinical diagnosis, clinical impression, and histopathologic diagnosis. All original hematoxylin and eosin (H&E) microscopic slides, accession sheets, and biopsy reports were reviewed. Results were aggregated and analyzed descriptively.

Results

A total of 212 cases were included in our database. The mean age was 61 years old, with an age range of 9 to 94 years. Of the 212 cases, 109 lesions were found in females and 103 lesions were found in males, with the female: male ratio of 1.06:1. Figure 1 shows the age distribution, in decades and the distribution by gender (n=210). The most common locations in descending order were the gingiva (n = 110 51.2%), palate (n=41, 19.3%), buccal mucosa (n=18, 8.5%), tongue (n=20, 9.4%), vestibule (n=13, 6.1%), lip (n=4, 1.9%), floor of mouth (n=3, 1.4%), and not specified (n=1, 0.5%) The intra-oral locations are depicted in Fig. 2. None of the lesions were described as symptomatic and the lesions were most frequently pink in color. The duration was not provided for about half of the lesions, but when available, ranged from less than one month to greater than 5 years. The lesions were most commonly reported as being present for an average of one to 5 months (n=52, 24.5%).

The most common clinical description provided was bumpy, rough, verrucoid and/or papillary. The clinical impressions in descending order were papillary lesion (squamous papilloma and verruca vulgaris) (n=67, 31.6%) followed by not specified or unknown (n=41, 19.3%), hyperkeratosis (n=24, 11.3%), fibroma (n=20, 9.4%), leukoplakia (n=17, 8.0%), dysplastic lesion (n=13, 6.1%), pyogenic granuloma (n=7, 3.3%), granulomatous reaction (n=5, 2.4%), lichen planus and VX (n=4 each, 2.0%), pigmented and other lesions

Fig. 1 Bar graph distribution of oral VX by gender (n = 210) and by age (decades of life)

Fig. 2 The intra-oral locations of the case series (n=212). Intra-oral photographs courtesy of Drs. Michael Kelly, James Wilson, Chad Marshall, Mary Hartigan, and Steven Hinze

(n=3 each, 1.4%), and salivary and periapical lesions (n=2 each, 0.9%).

All slides were reviewed and evaluated for histologic features consistent with VX including: papillary or verrucous proliferation of squamous epithelium, elongated rete ridges, and presence of aggregates of well-defined foamy *xanthoma cells* within the connective tissue papillae [13, 14] (Figs. 4 and 5). All three of these prominent microscopic features were identified microscopically and the definitive diagnosis of VX was rendered for all 212 lesions in this case series. Three of the 212 reported lesions were diagnosed as recurrences based on history.

Discussion

A comprehensive literature review was completed using the terms “oral verruciform xanthoma”. We identified and reviewed more than 70 publications related to oral VX. Large numbers of VX have been reported by several authors, among them Tamiolakis et al. [15] and Philipsen et al. [13].

Etiology

The etiology and pathogenesis of VX remains unclear, with a number of studies investigating the molecular structure and immunoprofile of these lesions [11]. However, two main hypotheses have been proposed in the literature. Zegarelli et al. suggested that the accumulation of lipid-containing macrophages might result from epithelial cell degeneration with release of the lipid material, which is scavenged by the macrophages [16]. The second hypothesis offered by Nowparast et al. suggested that the verrucous and papillary epithelial architecture seen in VX is probably secondary to the presence of foamy cells, which affect the metabolism of the epithelial cells, leading to a hyperkeratotic change [17]. Both hypotheses support a mutual interaction among macrophages, keratinocytes, and chronic inflammation. We noted significant sub-epithelial chronic inflammation in all our cases which lends support to the inflammatory hypothesis as the main etiology in the development of oral VX.

Clinical Features

Oral VX are frequently papillary lesions and rarely exceeds 2 cm in diameter [18, 19]. A slight male predilection has been reported in published literature. Tamiolakis et al., in their large and comprehensive review of the literature studied a total of 429 cases, including 412 garnered from the literature and 13 previously unpublished cases. They reported a female:male ratio of 1:1.4 in the 429 cases [15]. A female:male ratio of 1:1.1 was also reported by Philipsen et al. in their review of 159 cases [13]. In contrast to previous reviews, in our case series, we discovered a female: male ratio of 1.06:1.

Philipsen et al. also stated that in oral VX cases below the age of 50, the female: male ratio was 1:1.6 and that the ratio reverses after 50 in favor of females, with the female: male ratio of 1:0.8 [13]. Our data correlates with this finding, as seen in Fig. 1. Oral VX are most commonly seen within the 4th to 7th decade of life [20]. Our case series correlates with the published data with a mean age of 61 years and an age range of 9 to 94 years, as seen in Fig. 1.

Intra-oral Location

Oral VX are benign lesions that are observed exclusively on squamous epithelium. A review of the literature revealed that 70% were localized to anatomic regions that are continuously exposed to trauma, particularly the masticatory mucosa [19]. As seen in Fig. 2, in our study, a similar 70.8% ($n = 150$ of 212) of VX were located on the masticatory mucosa. Apart from the masticatory mucosa, i.e. gingiva and palate, VX may also be seen in other locations such as the tongue, the floor of the mouth, the vestibule and lips.

The second least common location in our case series was the lip with 1.89% ($n = 4$). The mucosal surface of the lips is a commonly exposed site to trauma. Importantly, oral VX are rarely reported to extend to cutaneous surfaces, areas not as likely to be traumatized. However, along with other studies, our study also had rare cutaneous VX [21–26]. Floor of the mouth is an even more unusual location for VX [21] with 1.42% ($n = 3$) lesions seen in here. Contrary to cutaneous xanthomas, oral VX are not associated with hyperlipidemia or underlying disease, such as xanthelasma palpebrarum, hyperlipidemia, and juvenile xanthogranuloma [11].

Clinical Differential Diagnoses

The most common lesions included in the clinical differential diagnosis includes squamous papilloma, verruca vulgaris, fibroma, leukoplakia, and squamous cell carcinoma [27]. In our series, only four cases were clinically suspected as VX. Most lesions in this series, the clinical impressions were identified clinically as papillary ($n = 67$, 31.6%). As seen in Fig. 3, all the gingival VX exhibit a papillary growth, but VX is frequently overlooked in the differential diagnosis of papillary lesions of the gingiva.

Due to a predominantly papillary architecture, the possibility of transmissible viral etiology should be considered in the differential diagnoses. Several studies have explored the role of human papillomavirus (HPV) in VX. Only one HPV positive case of VX of the scrotal skin has been reported by Khaskhely et al. who detected HPV by immunohistochemical, electron microscopy, and PCR amplification [28]. However, no reported significant relationship between oral VX and HPV has been established employing in situ hybridization and immunohistochemical studies [29].

Histologic Features

The definitive diagnosis of oral VX is accomplished through microscopic examination frequently following an excisional biopsy. The most common microscopic features, include: (1) papillary or verrucous proliferation of squamous epithelium, (2) elongated rete ridges, (3) presence of aggregates of well-defined lipid-laden *xanthoma*

Fig. 3 Intra-oral photographs of verruciform xanthoma (VX) located on the gingiva, exhibiting a papillary growth pattern: **a** Photo courtesy of Dr. Lee Hauer. **b** Photo courtesy of Dr. Leah Strange. **c** Photo courtesy of Dr. Esther Oh. **d** Photo courtesy of Dr. William McKenzie. **e** Photo courtesy of Dr. Indraneel Bhattacharyya. **f** Photo courtesy of Dr. Daniel Mullett. **g** Photo courtesy of Dr. Russell Walther. **h** Photo courtesy of Dr. Steven Fontana

cells within the connective tissue papillae [8, 9], (4) significantly thickened parakeratin with a frayed surface and prominent “orange coloration” which shows a sharp demarcation from the remaining epithelium [30], (5) parakeratin clefting into the underlying spinous layer [10] and (6) chronic inflammation of varying degrees in the subjacent lamina propria [9]. As seen in Fig. 4, a variety of histologic presentations are seen and moreover, these histologic variations are not dependent on the location or the duration of the lesion. For example, both **e** and **f** from Fig. 4 were located on the gingiva, with varying amount of thickness of the surface epithelium. Also, both **g** and

Fig. 4 Variation of histologic presentation of VX H&E (hematoxylin and eosin staining): **a** Abundant xanthoma cells ($\times 5$ magnification). Inset ($20\times$ magnification). **b** Minimal xanthoma cells ($\times 5$). Inset ($20\times$ magnification). **c** Nodular lesion ($\times 5$ magnification). Inset ($20\times$ magnification). **d** Prominently papillary lesion ($\times 5$ magnification). Inset ($7\times$ magnification). **e**—Relatively flat lesion ($\times 5$ magnification). Inset ($15\times$ magnification). **f** A typical histopathologic (classic) example ($\times 5$ magnification). Inset ($15\times$ magnification). **g** Presence of abundant keratin on the surface ($\times 5$ magnification). Inset ($15\times$ magnification). **h** Variant with minimal surface keratin ($\times 5$ magnification). Inset ($10\times$ magnification)

h from Fig. 4 were located on the lateral surface of the tongue, with varying amounts of parakeratosis.

In 1981, Nowparast et al. described three different architectural types of oral VX as viewed under low-power [17]. These architectural subtypes (a—*verrucous type*, b—*papillary type*, and c—*flat type*) can mimic other papillary entities. Lesions of the first variety, the *verrucous type* (a) are

hyperkeratotic, well circumscribed, acanthotic, and usually elevated. The parakeratin forms invaginating crypts that extend deep into the acanthotic epithelium. In some cases, the lateral rete ridges, taper toward the center, producing a cup-shaped appearance, mimicking verruca vulgaris and verrucous carcinoma, but do not show a thickened stratum granulosum. Examples of this mimicry can be seen in

Fig. 5b and c. The *papillary type* (b) has numerous stratified squamous epithelium finger-like projections with cores of connective tissue. Parakeratin covered crypt-like spaces extend above the mucosal surface, similar to a papilloma. These lesions can mimic squamous papilloma, viral papilloma, and inflammatory papillary hyperplasia. Examples of this subtype can be seen in Fig. 5a and e. The possibility of misdiagnosis exists if the xanthoma cells are overlooked. In the last variety *flat type* (c), the epithelial proliferation is seen below the surface. The rete ridges which are slender and of uniform depth exhibit variable elongation. The connective tissue papillae may extend close to the surface and is separated from the outer surface by a thin, minimally parakeratotic cell layer. Parakeratosis varies with the different patterns; Nowparast et al. reported a more intense parakeratosis in the verrucous and papillary types [17]. Lesions of the *flat type* (c) can mimic fibromas, lichen planus, and non-verrucoid dysplastic changes. The flat subtype of VX can be

seen in Fig. 5d and f with the epithelial proliferation below the surface and a flat or uniform depth of the rete ridges.

Immunohistochemistry

Previous studies report that immunohistochemical stains can be used to aid in the diagnosis of VX, including CD68, CD63 and CD163. Mostafa et al. first reported that the clone PG-M1 of the monoclonal antibody—CD68 identifies macrophages [31]. The other immunohistochemical stains, CD63 and CD163 (monocytic/macrophage markers), expressed on the majority of circulating macrophages and monocytes are positive for the *xanthoma cells* as well. The *xanthoma cells* have been reported to stain negatively for S100, CK8, CK19, CK14, and pankeratin [8, 15]. No immunohistochemistry was performed in our study since the diagnosis was rendered on the basis of histopathologic features alone.

Fig. 5 Histologic differential diagnosis (H&E) and VX mimicking various other lesions: **a** VX mimicking of inflammatory papillary hyperplasia ($\times 3$); Inset ($20\times$)—numerous papillary projections covered by hyperplastic, stratified squamous epithelium. **b** VX mimicking of verruca vulgaris ($\times 5$); Inset ($15\times$)—proliferation of hyperkeratotic stratified squamous epithelium arranged in fingerlike projections and prominent cupping effect. **c** VX mimicking of verrucous carcinoma ($\times 3$); Inset ($10\times$)—deceptively benign appearance with lengthened rete ridges that “push” into the underlying connective tissue and prominent parakeratin clefting. **d** VX mimicking of dysplastic changes ($\times 5$); Inset ($20\times$)—well-differentiated squamous epithelium with broad, blunt rete ridges featuring hyperchromatism. **e** VX mimicking of viral papilloma ($\times 2$); Inset ($15\times$)—thin connective tissue cores supporting blunted and broad papillary projections. **f** VX mimicking of a fibroma ($\times 5$); Inset ($15\times$)—nodular shaped mass with interconnecting fibrous rete ridges

Treatment

Treatment consists of simple excision and excellent prognosis is reported [13]. Colonna et al. do not advocate cryosurgery and reported that VX are resistant to such treatment [23]. The majority of the specimens in this study were from a diverse group of clinicians and as a result treatment and outcome data were not available. Recurrence of oral VX have been reported as extremely rare. In our case series, only three cases were recurrent, by history, however, follow-up data was not available in majority of the cases. The recurrent cases were from the lower lip, the maxillary gingiva, and the mandibular vestibule.

Conclusion

To the best of our knowledge, this is the largest case series of oral VX (n = 212) with detailed analysis of relevant literature, demographics, clinical appearance, and histologic presentations. Our findings are mostly consistent with those reported in literature. Only four cases were clinically suspected as VX, demonstrating the unfamiliarity of VX among clinicians. This case series illustrates the need for expansion of differential diagnoses of papillary lesions of the oral cavity to include verruciform xanthoma.

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