Verruciform Xanthoma: A Retrospective Clinical and Histopathologic Analysis of 90 Cases

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Short Running Title: Verruciform Xanthoma: A Report of 90 Cases

ABSTRACT

Objective: This study retrospectively investigated the clinical and histopathological findings of lesions diagnosed as Verruciform Xanthoma (VX) by the Louisiana State University Oral Pathology Biopsy Service from 1970 to 2014.

Study Design: A clinical and histopathologic evaluation was completed for 99 cases. A questionnaire was sent to surgeons who performed the biopsies from 1994 to 2014 to obtain further patient information regarding recurrence, tobacco use, oral health history, and history of oral trauma.

Results: After histopathologic evaluation, 90 confirmed cases of VX were included in the study. Males made up 57.3% of the cases. The mean age was 56.6 and was most common in the 6th

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through 8th decades of life (57.8%). Most common location was the gingiva (47.8%) with 58.1% of the gingival lesions occurring in the mandible. Inflammation was present in 97.8% of the cases with varying severity. Foam cells were found below the rete ridges 23.3% of the time. There was one confirmed recurrence. Seventy percent of the time mitotic figures were detected. Only four clinicians reported any history of trauma in the area of the biopsy. Three patients admitted tobacco use.

Conclusions: VX is a rare, benign, slow growing lesion with unknown etiology and low recurrence that commonly affects patients between the 6th and 8th decade of life. Histopathologically these lesions often present with varying degrees of inflammation, hyperparakeratosis, and foam cells between or below the rete ridges. The presence of mitotic figures may be an indication of the etiology or pathogenesis of these lesions.

Introduction

Verruciform xanthoma (VX) is a rare, benign lesion of the oral mucosa with unknown etiology which was first reported by Shafer in 1971 as a series of 15 cases [1]. Other extra oral sites of development include the vulva [2], penis [3,4], scrotum [5,6,7], and esophagus [8,9]. Current data regarding the prevalence of oral VX is minimal, with Buchner et al. reporting 6 cases out of 24,426 from Oral Pathology Diagnosis Services of University of California from 1968-1980. [14,21]. Clinically VX most commonly presents as a slightly elevated, slow growing, asymptomatic lesion with a rough surface architecture [10]. Lesions have been reported as pink, yellow, red, or gray in color and reportedly range from 1-25 mm [10,12]. VX most often develops on the gingiva and alveolar ridges, however lesions may develop at any intraoral location [11,12]. Given the clinical presentation, the differential diagnosis typically includes squamous papilloma, verruca vulgaris, condyloma acuminatum or possibly squamous cell carcinoma [13,28].

Gender predilection data has varied with some authors finding a slight male predominance and others reporting a slight female predilection [11,12,14]. Previous studies have found that VX can occur over a wide age range, however it is most commonly diagnosed in the fourth to sixth decades of life [12,14]. VX is treated with surgical excision [1] and a limited number of recurrences have been documented [11,12,15]. While the majority of VXs occur in patients who are otherwise healthy, cases have been reported in patients with various inflammatory disorders including discoid lupus erythematosus, pemphigus vulgaris, epidermal dysplasia, bone marrow transplantation, graft-versus-host disease and lichen planus [13,35,36].

Biopsy with histopathologic examination is required to establish a diagnosis of VX. Lesions generally exhibit papillary, hyperplastic stratified squamous epithelium surfaced by a prominent layer of parakeratin. Some have described the parakeratin as having an orange color on hematoxylin and eosin (H&E) staining [11]. The parakeratin may fill crypts between the papillary epithelial projections. Although most lesions exhibit a prominent papillary architecture, some may have a more flat surface. Nowparast et al classified VX into three morphologic subtypes: verrucous, papillary, and flat [12]. Another diagnostic feature is the presence of macrophages with foamy cytoplasm (foam cells or xanthoma cells) within the connective tissue papillae and occasional extension below the level of the rete ridges. [12]. The foam cells are believed to represent inflammatory macrophages based on positive staining with monocyte-macrophage biomarkers including CD68 [18,19]. Additionally, these foam cells stain positively with Periodic Acid-Schiff (PAS) and are diastase resistant [16].

Although there have been many single case reports of VX, few large series have been published. The largest case series are Nowparast et al (54 cases), Ide et al (36 cases), and Neville and Weathers (21 cases) [12,31,11]. The purpose of this study was to examine 90 VX cases diagnosed at the Louisiana State University School of Dentistry (LSUSD) Oral Pathology Biopsy Service between January 1, 1970 to December 31, 2014. Available patient demographics were recorded and additional data received from a follow-up questionnaire to

clinicians who submitted the biopsy was collected. A detailed histopathologic analysis of all specimens was performed.

Materials and Methods:

This project was approved by the Louisiana State University Health Sciences Center Institutional Review Board. Ninety-nine cases diagnosed as VX were identified through a search of the LSU Oral Pathology Biopsy Service database from January 1, 1970 to December 31, 2014. Pathology request forms submitted with the specimens, glass slides and pathology reports were collected and reviewed. Nine cases were excluded due to degraded slide quality or lack of definitive diagnostic features. The 90 remaining cases were included in the study.

The following clinical and demographic features were collected: age, gender, race, location of lesion, size of specimen. A questionnaire was mailed to all clinicians who submitted biopsies between 1994 and 2014. Because records are not generally required by law to be kept for more than 7 years post treatment, the likelihood of record availability for cases submitted samples submitted prior to 1994 was presumed to be low. The purpose of the questionnaire was to gather more information regarding history of trauma at the site of the VX, recurrence, use of tobacco products, and presence of other mucosal lesions.

All H&E-stained glass slides were initially reviewed by a third year periodontics resident and subsequently assessed by two board certified oral and maxillofacial pathologists. Each case was evaluated for the following features: papillary or flat architecture, presence of ulceration, parakeratosis, hyperkeratosis, location of foam cells (between rete ridges only or extension beyond rete ridges), location and intensity of inflammation, and quantity of epithelial mitotic figures per 5 high power fields (HPF, 40x). Frequency of mitoses was divided into three categories: absent (none observed per 5 HPF), less than 3 per 5 HPF, or 3 or more per 5 HPF.

Results:

A total of 90 cases diagnosed as VX from the LSUSD Oral Pathology Biopsy Service archives were analyzed. Of the 67 questionnaires sent, 39 responses (58.2%) were received, 21 of which indicated records were available.

Patient Demographics

Patient age ranged from 14-94 with a mean of 56.6 years old. Age was not reported in two cases. VX was found to be most common in the sixth through eighth decades, accounting for 57.3% of all cases (See table 5). The mean age for males was 54.7 and the mean for females was 59.3. Males represented 57.8% of the samples. Gender was not reported in one case. The great majority of the cases were from patients of Caucasian decent (90.0%), African Americans comprised 5.6%, and race was not reported in four cases (4.4%).

Location and Size

VX occurred most often on the gingiva (47.78%), followed by the hard palate (27.78%), buccal mucosa (11.11%), and the tongue (6.67%). Location was not reported in one case. Gingival lesions were more common on the mandibular mucosa (58.1%) than the maxillary mucosa (39.5%). One case did not specify mandibular or maxillary location. Size was designated as the largest dimension according to the gross measurement. Specimens ranged from 3 mm to 17 mm with the average being 7.8 mm.

Histopathologic presentation

All specimens were non-ulcerated and surfaced by parakeratin with 73% exhibiting hyperparakeratosis. The majority of samples (82.2%) had a papillary architecture whereas 16.7% had a flat morphology. The presence of epithelial mitotic figures were as follows: absent in 30% of cases, less than 3 per HPF in 59% of cases, and 3 or more in 11% of cases.

In 75.6% of cases, the diagnostic foam cells were located between rete ridges only. In 23% of cases, foam cells were observed both between the rete ridges and extending into the lamina propria below the level of the rete ridges. All but one case (2.2%) had inflammation. Inflammation was limited to the connective tissue in 52.2% of cases and was seen in both the connective tissue and the epithelium in 45.6% of cases. The intensity of inflammation was heavy in 21.1%, moderate in 37.8% and mild in 38.9% of cases.

Questionnaire Results

Four of the 21 returned surveys (19%) indicated that the patient had a history of trauma in the area where the VX was found. One biopsy confirmed recurrence was reported one year after the initial biopsy. Another clinician reported a “white area in the healing site” but the lesion was not biopsied to confirm or exclude recurrence. Three patients had a reported history of tobacco use (one cigarette, one smokeless, and one who reported using both). Additional oral lesions identified in patients with VX included: tobacco keratosis, lichen planus, hyperplastic gingiva, unidentified papillary lesions, and amalgam tattoo. Additional reported findings and conditions included alcohol abuse (1), Sjogren syndrome (1), xerostomia (1), and phenytoin use (1).

Discussion:

Since the first publication of VX by Shafer 1971 [1], the etiology is still yet to be determined. Two prevailing hypothesis have been formulated in the literature. Zegarelli et al suggested that localized chronic trauma causes epithelial degradation and release of lipids that are then phagocytized by macrophages [32]. Nowparast et al hypothesized that foam cells are present first and affect epithelial metabolism which results in papillary changes [12]. In the present study the first hypothesis seems to be the most likely. The majority of oral lesions seen here were found on keratinized tissues (Table 1 and 2) that are typically more prone to trauma.

The presence of some degree of histologic inflammation in almost all samples also supports a potential traumatic etiology. However, previous authors have stated that if the main etiology of VX is trauma then lesions would be far more common and trauma alone would not explain VX that occur on areas not prone to trauma [14].

In the present study history or presence of other oral mucosal lesions seemed to be unrelated to VX in this patient population. There was only one confirmed case of recurrence in this study of a mandibular gingival lesion one year after the initial removal of the lesion. This is consistent with a low recurrence rate found in the literature, with only three reported cases of recurrence since VX had been first described in 1971 [12,15,34].

The present study found a slight male predilection which is consistent with other case series [10,12,14,15,18,30]. Although the mean age at the time of biopsy was 56.6 years old, the majority of the cases in this case series are from patients coming between the 6th and 8th decades. This deviates from previously published research that showed VX lesions being more common in the 4th through 6th decades [11,12,14,15,18,30,33]. The majority of cases of VX were from Caucasians, which is similar to other studies [11,12].

Microscopic characteristics of oral VX including papillary epithelial hyperplasia, a superficial layer of orange parakeratin, and sub-epithelial presence of lipid filled macrophages have been well established [15,19]. Nowparast et al further subdivided VX lesions into three categories based on their histologic presentation: verrucous, papillary, and flat. The verrucous form appears elevated with well circumscribed borders and lacks a thick granular layer as seen in verruca vulgaris and also exhibits signs of hyperkeratosis, acanthosis, and elongated rete ridges [12]. The papillary form is characterized histologically by fingerlike projections of stratified squamous epithelium with connective tissue cores and cryptic spaces covered with parakeratin that extends above the mucosal surfaces but does not typically proliferate below the surface [12]. The flat form exhibits epithelial proliferation below the surface with periods of elongated rete ridges that are flat and of uniform depth [12]. Though several case studies following the

Nowparast publication categorized their samples into these categories [30,31,33], the present study did not. Upon review of the 90 cases included here, it was too difficult to categorize based on verrucous, papillary, or flat because each case displayed characteristics of some or all of these types in any given case.

The hallmark of VX is the presence of foam cells. Early publications indicated that foam cells were not present below the rete ridges [1,8,11], although more recent studies found a small percentage of foam cells below the rete ridges in the lamina propria [12,31,34]. Our study found that foam cells were present below the rete ridges 23.3% of the time which is far more common than previous reports.

The etiology at this time is still unknown, although based on the location and presence of inflammation noted in this case series, trauma appears to be the most probable causative agent. Several publications have explored a possible link between VX and the HPV virus but these studies have been limited to small sample case studies. In 1993, Helm et al. discussed a single case of oral VX in an immunocompromised patient in which in situ testing for HPV types 6/11, 16/18, 31, and 33 were negative for HPV [26]. Iamaroon and Vickers examined 12 retrospectively collected cases of oral VX and found, via in situ hybridization, that only one case tested positive for HPV types 6/11 and none tested positive for the HPV antibody [15]. Hu et al. also failed to detect HPV (types 6, 11, 16, and 18) in three oral VX cases using the in situ hybridization method [27].

Although these specific types of HPV have previously been evaluated as a potential etiologic factor, the published results are not consistent with the virus having a major role in the pathogenesis of VX. Other hypothesized etiologies support that VX could be a multifactorial reactive process (trauma, tobacco/alcohol, allergies, and dental materials) [31], caused by a local T-cell mediated immunologic disorder [18], or an immunologic response similar to lichen planus [10].

The majority of the flat lesions were located on the gingiva (46.7%) and palate (26.7%). Of the 16% of the samples with a flat architecture, 80% had sparse mitotic figures which was higher than the rest of the sample. In this group, inflammation was mostly present in the connective tissue (73.3%) compared to the sample average of 48%. Among cases with 3 or more mitoses per 5 HPF, 80% had heavy inflammation and 90% had hyperparakeratosis. The most common location for lesions with 3 or more mitoses per 5 HPF was the hard palate (60%). It remains to be seen what the significance of the mitotic figures is with regards to pathogenesis of VX but this could be an indication of etiology.

Conclusion:

VX is a rare, benign lesion that is most common in Caucasian males. It most often presents between the 6^{th} and 8^{th} decade. Recurrence of VX is presumed to be rare following surgical excision. Etiology is still yet to be determined but strong evidence suggests that it is a reactive lesion in response to localized trauma. Presence of inflammation and mitotic figures in conjunction with foam cells may further support the theory of trauma.

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Tables

1.

Location	**Number (n)**	**Percent (%)**
Gingiva	43	47.8%
Hard Palate	25	27.8%
Buccal Mucosa	10	11.1%
Tongue	6	6.7%
Lip	2	2.2%
Floor of mouth	1	1.1%
Vestibule	1	1.1%
Soft Palate	1	1.1%
Not reported	1	1.1%

2.

Gingival lesions	**Number (n)**	**Percent (%)**
Maxilla	17	39.5%
Mandible	25	58.1%
Non-specific "alveolar ridge"	1	2.2%

3.

Age	<29	30-39	40-49	50-59	60-69	70-79	80+
M (51)	5	7	6	12	8	9	4
F (36)	2	3	5	6	8	8	4
UNK Gender					1		

4.

Age	<29	30-39	40-49	50-59	60-69	70-79	80+
Sample (n = 88)	7	10	11	18	17	17	8
Percent (%)	8.0%	11.4%	12.5%	20.5%	19.3%	19.3%	9.1%

5.

Age	<29	30-39	40-49	50-59	60-69	70-79	80+	Unknown
Sample (n = 90)	7	10	11	18	17	17	8	2
Percent (%)	7.8%	11.1%	12.2%	20.0%	18.9%	18.9%	8.9%	2.2%

6.

	Number	**Percent**
Mitotic figures		
Not detectable	27	30.0%
< 3 per HPF	53	58.9%
≥ 3 per HPF	10	11.1%
Inflammation location		
Connective tissue	48	52.2%
Epithelium	0	0%
Epithelium and Connective tissue	41	45.6%
Not present	2	2.2%
Inflammation severity		
Mild	34	37.8%
Moderate	34	37.8%
Heavy	19	21.1%
Ulcerated epithelium		
Yes	0	0%
No	90	100%
Foam Cell location		
Between rete	68	75.6%
Lamina propria	0	0%
Between rete and in Lamina propria	21	23.3%
Papillary architecture		
Yes	74	82.2%
No	15	16.7%
Surface Keratinization		
Parakeratin	90	100%
Hyperperakeratin	66	73.3%

7.

	Present study (90)	Nowparast (54)	Ide (36)	Neville (21)	deAndrade (20)
Location	Gingiva 47.78% Hard palate 27.78% Buccal mucosa 11.11% Tongue 6.67%	Masticatory mucosa 42.59% Hard palate 29.63% Tongue 11.1% Buccal mucosa 5.6%	Gingiva/alveolar mucosa 69.4% Tongue 11.1% Buccal mucosa 8.3% Palate 8.3%	Gingiva/alveolar ridge 64% Mucobuccal fold or buccal mucosa 23.8%	Hard palate 30% Buccal Mucosa 30% Gingiva 25% Floor of mouth 10% Buccal vestibule 5%
Mean Age (Range)	56.6 (14-94)	51 (14-89)	58.3 (27-84)	48 (18-80)	50 (28-74)
Gender Predilection	M>F (1.4:1)	M>F (1.7:1)	M>F (1.6:1)	M<F (1:1.5)	M>F (1.5:1)
Race	Caucasian 94.2% African-American 5.8%.	Caucasian 96.3% African-American 1.9% Other 1.9%	Not reported (Japanese study)	Caucasian 94% African-American 6%	Not reported (Brazilian study)
Size (Range)	3-17 mm	2-20 mm	Not Reported	2-20 mm	1-25 mm

Figure 1

Verruciform Xanthoma Retrospective Analysis Questionnaire, IRB: # 8917

Regarding: Patient (Last, First): _____
Date of Birth/Age: _____
Date of biopsy: _____
LSU Specimen Number: _____

If the above patient records are no longer available please place a checkmark below:
_____Records no longer exist for the patient in question

- Are you aware of another clinician who may have this information? If so please provide the name of that doctor and potential contact information:
  _____

If patient records are available please complete the following:

- **This patient was last examined on:** _____
- **Was there any history of trauma in the location where lesion initially appeared?**
  Yes: _____ No: _____
  If yes please describe nature of trauma:
  _____
  _____
- **Any evidence or report of recurrence of the lesion?**
  Yes: _____ No: _____
  If Yes, please specify as follows:
  Number of recurrences: _____
  Dates of recurrences: _____
- **Does the patient report a history of using of tobacco products?**
  Yes: _____ No: _____
  If yes, please specify as follows:
  Type of tobacco product: _____
  Duration of use: _____
- **Has the patient had any other oral mucosal lesions? (i.e. lichen planus, geographic tongue)**
  Yes: _____ No: _____
  If yes, please specify as follows:
  Type of lesion: _____
- **Any additional comments:**
  _____
  _____