Oral Verruciform Xanthoma: A Clinicopathologic Study of 15 Cases

Chuan-Hang Yu, Tung-Chieh Tsai, Jeng-Tzung Wang, Bu-Yuan Liu, Yi-Ping Wang, Andy Sun, Chun-Pin Chiang*

Background/Purpose: Oral verruciform xanthoma (VX) is an uncommon oral mucosal lesion. This retrospective study evaluated the clinical and histopathologic features of 15 oral VXs occurring in Taiwanese patients.

Methods: Fifteen consecutive cases of oral VX were collected from January 1988 to December 2005. Clinical data and microscopic features of these cases were reviewed and analyzed.

Results: The mean age of patients was 45 years (range, 18–79 years). There were eight male and seven female patients. Seven (46.6%) cases occurred on the gingiva, four (26.7%) on the tongue, and four (26.7%) on the buccal or vestibular mucosa. The greatest mean dimension of the lesions was 0.8 cm (range, 0.3–2.0 cm). Three patients had concomitant other oral mucosal lesions such as oral submucous fibrosis, squamous cell carcinoma, and erosive oral lichen planus. Microscopically, all specimens showed varying degrees of surface parakeratosis and the accumulation of numerous foam cells in the connective tissue papillae among uniformly elongated epithelial ridges. Individuals or aggregates of foam cells were also found underneath the epithelial ridges in nine (60%) cases. When the oral VX lesions were further classified into three types according to the microscopic surface architecture, seven (47%) lesions were of the verrucous type, three (20%) the papillary type, and five (33%) the flat type. All patients received surgical excision of the lesions and no recurrence was noted during follow-up of up to 18 years.

Conclusion: Oral VXs occur more frequently in the fifth decade of life. The more commonly affected site is the gingiva. The treatment of choice for oral VXs is surgical excision. The prognosis is excellent and recurrence was not seen in this study. [J Formos Med Assoc 2007;106(2):141–147]

Key Words: clinical feature, histopathologic feature, oral verruciform xanthoma

Oral verruciform xanthoma (VX) is an uncommon oral mucosal lesion that was first described by Shafer in 1971.1 The frequency of occurrence is approximately 0.025%.2 Up to 2001, a total of 282 cases of oral VX have been reported.3 Oral VXs occur more often in middle-aged patients with a mean age of 51 years.4,5 There was a slight male predilection in the largest series of 282 cases reported.3 The most frequent site of occurrence is the gingiva.3,4

Clinically, oral VX appears as a small, asymptomatic, verrucous, papillary, or flat lesion with a white, yellow-white, or red color depending on the degree of surface keratinization and the number of lipid-laden macrophages in the connective tissue papillae.6 The papillary or verrucous outer appearance of the lesion with a broad or pedunculated base often leads to a clinical misdiagnosis of papilloma, verrucous hyperplasia, verrucous carcinoma, or squamous cell carcinoma (SCC).7

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Microscopically, the lesion is characterized by varying degrees of parakeratosis, parakeratin plugging, and numerous foam or xanthoma cells accumulated within the connective tissue papillae among uniformly elongated epithelial ridges. The etiology and pathogenesis of oral VX remain unclear, while inflammatory, viral, and immunologic factors have been suggested. Viral factor is less likely because in situ hybridization study shows that < 10% of VX specimens are human papillomavirus (HPV) DNA-positive and none of the VX specimens are HPV antigen-positive. Although several large-series studies of oral VX have been reported in the West, only two cases of oral VX have been reported from Taiwan in the English literature. Therefore, the purposes of this study were to describe the clinical and histopathologic features of 15 oral VXs occurring in Taiwanese patients and to compare our results with those from previous studies.

Methods

The study group consisted of 15 cases of oral VX retrieved from the files of the Department of Oral Pathology and Oral Diagnosis, National Taiwan University Hospital, Taipei, from January 1988 to December 2005. All lesions received an excisional biopsy. The biopsy specimens were fixed in 10% neutral formalin for at least 24 hours, dehydrated in graded alcohol, and then embedded in paraffin. The paraffin-embedded tissue blocks were cut in serial sections of 5 μm, which were then stained with hematoxylin and eosin (H&E) and examined by microscopy. Histopathologic diagnosis of the lesion was based on examination of the H&E-stained tissue sections.

The characteristic microscopic criteria for diagnosis of oral VXs included parakeratotic, acanthotic epithelium with verrucous, papillary, or flat outer surface, uniformly elongated epithelial ridges, and the accumulation of a large number of lipid-laden macrophages (xanthoma cells) in the connective tissue papillae. The oral VXs were further classified into three types according to the microscopic surface architecture proposed by Nowparast et al.: type A (verrucous), type B (papillary), and type C (flat).

Data on patients' age, gender, location and size of lesion, clinical diagnosis, treatment, and oral habits (OHs) of the patients were obtained by reviewing the dental charts. Other oral mucosal lesions occurring concomitantly with oral VXs were also recorded.

Results

The clinical data of the 15 oral VXs are presented in Table 1. The mean age of patients at the time of diagnosis was 45 years (range, 18–79 years). There were eight male and seven female patients. Of the 15 VXs, seven (46.6%) occurred on the gingiva (4 on mandibular and 3 on maxillary gingivae), four (26.7%) on the tongue (Figure 1, patient 13), and four (26.7%) on the buccal or vestibular mucosa. The greatest mean dimension of the lesions was 0.8 cm (range, 0.3–2.0 cm). Only three lesions were correctly diagnosed as oral VX at the time of initial clinical presentation. Verrucous hyperplasia (5 cases) was the most common initial clinical diagnosis, followed by papilloma or papillomatous lesion (3 cases), ulcerative lesion (2 cases), fibroepithelial polyp (1 case), and exophytic mass (1 case) (Table 1).

Data on OHs (alcohol drinking, areca quid chewing, cigarette smoking) were available for 13 patients. Seven patients had no OH and six had at least 1 OH (3 with 3 OHs, 1 with 2 OHs, and 1 with 1 OH) (Table 1). Three patients had concomitant oral mucosal lesions such as oral submucous fibrosis (OSF), SCC, and erosive oral lichen planus (EOLP) at independent sites. All patients received excision of the lesion and no recurrence was noted during follow-up of up to 18 years.

The histopathologic features of the 15 oral VXs are summarized in Table 2. All 15 specimens showed varying degrees of surface parakeratosis and the accumulation of numerous foam cells in
the connective tissue papillae among uniformly elongated epithelial ridges (Figure 2A). Parakeratin plugs were also frequently found extending from the surface into the crypts formed by epithelial projections (Figure 2B). Although foam cells were uniformly found in the connective tissue papillae in every VX case, individuals or aggregates of additional foam cells were also found underneath the epithelial ridges in nine (60%) cases. When the 15 lesions were further classified into three types according to the microscopic surface architecture, seven (47%) lesions were of the verrucous type (Figure 2B), three (20%) the papillary type (Figure 2C), and five (33%) the flat type (Figures 2D and 2E).

There were varying degrees of acute or chronic inflammatory cell infiltrate in the subepithelial...
connective tissue. Of the 15 lesions, eight had mild, four had moderate, and three had severe degrees of inflammation. In the three lesions with severe inflammation, lymphocytes had aggregated to form germinal centers in the lamina propria (Figure 2E). Chronic inflammatory cell infiltrate composed mainly of lymphocytes and plasma cells was noted in all 15 lesions. Acute inflammatory cell infiltrate composed predominantly of neutrophils and eosinophils was found in eight lesions. Only one lesion presented a neutrophil-dominant infiltrate. In the other seven lesions, neutrophils or eosinophils were sparsely distributed among chronic inflammatory cells.

Discussion

The mean age of our 15 patients with oral VX was 45 years and six (40%) of our 15 patients were in their fifth decade of life. Several previous studies also noted that the mean age of patients with oral VX was between 40 and 49 years. However, mean patient ages of older than 49 years or younger than 40 years have also been reported. The discrepancy in the mean age of patients may be due to differences in the race of patients and sample size.

In this study, oral VXs occurred nearly evenly in males and females. Two previous studies also
demonstrated an equal gender distribution of patients with oral VX. However, most previous studies showed either a slight male predilection or a female predominance for the occurrence of oral VXs. The differences in gender distribution of patients among these studies may suggest that there is probably no significant gender predilection in patients with oral VX.

In the largest series of 282 cases of oral VXs reported by Philipsen et al, the most commonly affected site was the gingiva (57.4%), followed by the tongue (10.3%), hard palate (7.1%), buccal or vestibular mucosa (6.7%), floor of the mouth (4.6%), and soft palate (3.2%). Other studies including ours also showed that the most common site was the gingiva. The size of oral VXs was usually between 0.2 and 2.0 cm, with the exception of the largest lesion measuring 4.0 × 1.5 cm documented by Graff et al. A comparable result in lesion size was also found in this study.

In the present study, only 20% (3/15) of oral VXs were correctly diagnosed at the time of initial presentation. Because oral VXs usually showed verrucous or papillary outer appearance, they were frequently misdiagnosed as verrucous hyperplasia (5 cases) and papilloma or papillomatous lesions (3 cases) in this study. It should be noted by the clinician that in our series oral VXs may have surface ulceration (2 cases) or may look like a fibroepithelial polyp (1 case).

Several previous studies reported an association of a previously occurring or a concomitant oral mucosal lesion with oral VX. These lesions include lichen planus, pemphigus vulgaris, carcinoma in situ, and SCC. In our series, there were three oral VXs that developed in association with a concomitant oral mucosal lesion such as OSF (patient 4), SCC (patient 8), and EOLP (patient 15). The nature of the simultaneous occurrence of the lesions with oral VXs was not clear, but evidence of oral VX being a precancerous lesion has never been reported.

There was only one report showing the association of OHs with the occurrence of oral VXs. Neville and Weathers reported a 65-year-old female snuff user who presented with an oral VX at the mandibular alveolar mucosa and an SCC at the floor of the mouth. In the present study, five patients were alcohol drinkers, five were areca quid chewers, and five were cigarette smokers. Because of the limited data on OHs in previously reported cases and the small sample size in this study, we could not draw a conclusion on the association of OHs with the occurrence of oral VXs.

Nowparast et al classified oral VXs into three types (verrucous, papillary, flat) according to the microscopic surface architecture of the lesions. In their series of 54 oral VXs, there were 24 (44%) lesions of the verrucous type, 17 (32%) of the papillary type, and 13 (24%) of the flat type. This study also showed that the verrucous type (7 cases, 47%) was the most common microscopic type. However, the flat type (5 cases, 33%) was the next most common and the papillary type (3 cases, 20%) was the least common.

The striking feature of oral VX is the accumulation of numerous foam cells (xanthoma cells) of varying sizes in connective tissue papillae. Previous studies have shown that these foam cells contain both lipid and periodic acid-Schiff (PAS)-positive, diastase-resistant granules in their cytoplasm. The origin of foam cells was found to be macrophages, because these foam cells are CD-68-positive and contain cathepsin B in their cytoplasm.

The etiology and pathogenesis of VX remains unclear. Based on light and electron microscopic studies, Zegarelli et al proposed that foam cells are lipid-laden macrophages and oral VX may develop as a consequence of epithelial entrapment with subsequent degeneration and lipid accumulation. They suggested a local irritant as the initiator of the disease process because oral VX is frequently found on masticatory mucosa where localized trauma is very common. Nowparast et al suggested that the verrucous and papillary architecture may be secondary to the presence of foam cells, which affect the nutrient and metabolism of the epithelial cells, leading to hyperparakeratotic change. Iamaroon and Vickers studied 12 cases of VX by in situ hybridization and
inflammatory cells were positive for HLA-DR suggested an immunologic pathogenesis for VXs. In VX lesions by anti-S-100 immunostaining and demonstrated the presence of Langerhans cells may play a role in VX pathogenesis. Rowden et al suggested that an immune response may play a role in VX pathogenesis. Rowden et al demonstrated the presence of Langerhans cells in VX lesions by anti-S-100 immunostaining and suggested an immunologic pathogenesis for VXs. Mostafa et al suggested that VX may be a local T-cell-mediated immunologic disorder. Oliveira et al suggested that the pathologic process of VXs may be based on an immunologic response similar to that of lichen planus. In addition, this study showed a universal presence of lymphocytes and plasma cells in all 15 oral VX lesions, the occurrence of all 15 oral VX lesions on easily traumatized mucosas such as gingiva, tongue, and buccal mucosa, the association of OHs with 46% (6/13) of oral VX lesions, and concomitant presence of oral epithelial lesions such as OSF, SCC, and EOLP in association with three oral VX lesions. Based on the findings from previous and present studies, we suggest that oral VX lesions may represent an immune-associated response to localized epithelial trauma or damage, resulting in the release of membranous lipid components into the adjacent connective tissue, phagocytosis of lipids by tissue macrophages, and the accumulation of lipid-laden macrophages in connective tissue papillae.

The treatment for oral VX is surgical excision and the prognosis is excellent. Recurrence is extremely rare. To date, only three recurrent cases have been reported in the literature, all located at the palate. In our series, all patients received surgical excision of oral VX lesions and no recurrence was observed during a follow-up of up to 18 years. In conclusion, oral VXs occur more frequently in the fifth decade of life. The most commonly affected site is the gingiva. The treatment of choice for oral VXs is surgical excision. The prognosis is excellent and recurrence is extremely rare.

References