CASE REPORT

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Verruciform xanthoma: Report of two cases and review on pathogenesis

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Abstract

Verruciform xanthoma [VX] is an uncommon benign mucocutaneous lesion of unknown etiology. This rare, harmless lesion usually presents as sessile or pedunculated, pale yellowish-to-red, papillary, granular or verrucous mucosal growth. Histologically VX is characterized by the presence of parakeratinzed epithelium showing papillary or verrucous growth with thin rete ridges and connective tissue papillae extending up to the surface. The papillae characteristically consist of foam cells, also called xanthoma cells. We report two cases of verruciform xanthoma and discuss their clinical and histopathological findings.

Keywords: Pathogenesis, verruciform xanthoma

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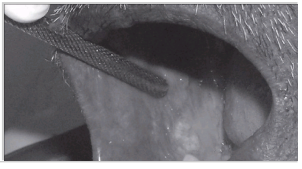

Introduction

Verruciform xanthoma [VX] is an uncommon benign lesion primarily of the oral mucosa, first described by Shafer in 1971. [1] Though VX has been identified in several parts of the body, extraoral VX was first described by Santa Cruz and Martin, who reported two vulval lesions. [2] Most frequently encountered sites for oral lesion are gingiva, alveolus, and hard palate. [3]

VXs are usually asymptomatic, solitary; though multifocal lesions have also been reported. They are slow-growing lesions; normal, red, or yellowish in color with sessile or pedunculated, papillary, granular or verrucous appearance. They rarely reach more than 1 cm in diameter. [4] Males are affected slightly more frequently than females. The majority of cases have been reported in Caucasians. [5]

Clinically VX needs to be differentiated from papilloma, verruca, verrucous carcinoma, and, sometimes, squamous cell carcinoma. Diagnosis is made on the basis of histological appearance of the lesions, showing hyperplastic parakeratinzed squamous epithelium with elongated rete pegs of relatively uniform depth. [6],[7] Nowparast *et al.* in their series of 54 cases of VX demonstrated three different architectural appearances of this lesion as seen under light microscope: A] a warty or verrucous appearance, B] a papillary or cauliflower architecture, and C] a slightly raised or flat lesion. [8]

The outstanding feature of the lesion is the presence of large swollen 'foam cells' or 'Xanthoma cells,' which fill the connective tissue papillae between the epithelial pegs. Underlying stroma shows mixed chronic inflammatory cell infiltration. [1] Only three recurrences have been reported so far. [5],[8],[9] Excision is usually the treatment of choice. [3] However, no potential for malignancy for this lesion has been reported in the literature to date.

Case History

Case 1

A 50-year-old man reported to the Institute of Dental Sciences, KLE University, Belgaum, with a chief complaint of dirty teeth. He gave a history of tobacco chewing 4 to 5 times a day since the last 15 years. Intraoral examination revealed a sessile, nonscrapable whitish yellow granular lesion measuring about 1 × 2 cm in diameter on the right buccal mucosa, which was nontender [Figure 1]. His oral hygiene was poor, with generalized stains and calculus. The patient was unaware of the lesion. Clinically the lesion was diagnosed as leukoplakia, and an excisional biopsy was preformed under local anesthesia.

Case 2

A 40-year-old man reported to the Institute of Dental Sciences, KLE University, Belgaum, with a chief complaint of missing teeth, for which he wanted replacement. He gave history of trauma to his lower jaw, inflicted 5 years back - later noting mobility of anterior teeth, which he reported were extracted. Intraoral examination revealed that 41, 42, 31, and 32 were missing. Two yellowish red slightly raised lesions on the lower labial mucosa near the mucogingival junction, measuring about 0.5 × 0.5 cm and 1 × 1 cm in diameter, were noted [Figure 2]. They were soft in consistency, nontender and not fixed to the underlying mucosa. The patient was unaware of the lesion. Clinically the lesion was diagnosed as hypertrophic Fordyce's spots, and an excisional biopsy was preformed under local anesthesia.

The lesions in these two cases showed similar microscopic appearance. Under low magnification, the section showed papillary projections lined by epithelium consisting of core of connective tissue [Figure 3]. Under higher magnification, the epithelium was parakeratinzed stratified squamous type with parakeratin plugging. Between the strands of epithelium, the connective tissue papillae extend up to the surface, with a thin layer of epithelium covering it. In these extensions, the stromal tissue appeared to be replaced by large cells [Figure 4]. Under higher magnification, these swollen cells showed clear-to-eosinophilic granular cytoplasm with eccentrically placed nuclei. These large swollen cells, also called 'foam cells' or 'xanthoma cells,' filled the connective tissue papillae between the epithelial pegs [Figure 5]. A mild-to-moderate degree of inflammatory cell infiltration consisting mainly of lymphocytes was observed in the stroma. Based on these histopathological features, diagnosis of verruciform xanthoma was given.

Discussion

In the biological profile of oral verruciform xanthoma [VX], based on a worldwide literature survey of 282 cases, it was seen that oral lesions of VX were mostly seen in males, with a male-to-female ratio of 1.1: 1. Below the age of 50, the male-to-female ratio was 1.6:1; and this ratio reversed after the age of 50 in favor of females, when the male-to-female ratio was 0.8:1. The most common location for VX reported is masticatory mucosa [73.4%], with gingival margin accounting for 85 [49.1%] cases. Next in order of frequency were hard palate [*n* = 25] [of these, 17 cases were contained in the 85 cases from gingival margin]; tongue [*n* = 16, of which 8 were localized to the dorsum/lateral border]; buccal mucosa/vestibular fold [*n* = 12]; floor of the mouth [*n* = 10] and attached gingiva/alveolar mucosa [*n* = 9]; soft palate [*n* = 8]; lower lip [*n* = 5]; junction between hard and soft palate [*n* = 3]. [3]

In 1961, Shafer first reported 15 cases of VX of the oral mucosa. [1] Although in most cases VX tends to occur as an isolated lesion, in several cases the lesion developed in association with other diseases, including snuff dipper's keratoses, [10] oral pemphigus vulgaris, [11] carcinoma *in situ,* [12] regressive dystrophic epidermolysis bullosa, [13] lichen sclerosus, [2] solar keratoses, [14] discoid lupus erythematosus, [15] epithelial nevus or epidermal nevus syndrome, [6] lichen planus [16] and congenital hemidysplasia with ichthyosiform erythroderma and limb defects [CHILD syndrome]. [17]

The lesion did not seem to be associated with systemic abnormality of lipid metabolism, with the exception of one case, which was associated with systemic lipid storage disease. That case was reported as a multifocal case, involving the tongue, larynx, epiglottis, right glottis, and peritonsillar mucosa. [18]

Zegarelli *et al.* 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. [19] Several authors have supported this theory. Zegarelli *et al.* suggested a 'local irritant' as the initiator of this process. [7],[9],[12],[20]

Discussing the epithelial hyperplasia with elongation of the epithelial rete ridges, Mostafa *et al.* suggested that this elongation is illusory and is not a proliferation of epithelial cells with downward growth of the rete pegs, 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. [21]

Nowparast *et al.* suggested that the verrucous and papillary architecture may be secondary to the presence of foam cells, which affect the nutrition and metabolism of the epithelial cells, leading to a hyperkeratotic change. These authors suggested that the lipid material found in the xanthoma cells could

be of the same nature as that found within foam cells in chronic inflammatory reactions such as dental granulomas and periapical cysts, where epithelial degeneration is common. [8],[22] Travis *et al.* also supported the view that the xanthoma cells are macrophages responsible for removal of lipid that accumulates in the submucosal tissues and that epithelial hyperplasia is a secondary event. Macrophages are known to produce a variety of growth factors that might play a role in inducing epithelial hyperplasia. [18]

Mostafa *et al.* observed that all xanthoma cells were negative for S-100 protein, which is in accordance with the results obtained by Rowden *et al.* S-100 protein-positive dendritic cells and Langerhans cells [LCs] have been found in the basal and suprabasal epithelium [melanocytes] by some investigators. Since both macrophages and LCs are known to be antigen-presenting cells, Mostafa *et al.* suggested that the migration of such a large number of macrophages towards the epithelium might be a compensatory phenomenon. [21]

Rowden *et al.* were of the opinion that VX belongs to a new category of 'non-X histiocytosis,' in which the presence of Langerhans cells suggested an immunological pathogenesis. [23] Mostafa *et al.* suggested that VX may be a local immunological disorder, most probably of cell-mediated mechanism, although the exact cause of this reaction could not be determined. Oliveira *et al.,* in a very recent report, suggested that the pathological process of VX may be based on an immunological response similar to that of lichen planus. [21]

A viral etiology has also been speculated since extraoral lesions usually occur in the genitalia. [24] Santa Cruz and Martin also suggested that a viral cause was possible, despite the lack of intraepithelial inclusions or pronounced vacuolation; and they recommended further ultrastructural examination of the epithelium for the presence of viral particles. Although many ultrastructural studies have been pursued, viral particles have not been seen in either the epidermal or epithelial cells. [2] Recently, three studies disclosed negativity for human papilloma virus in the lesions by using *in situ* hybridization. [18],[24] Many histochemical, immunohistochemical, and ultrastructural studies have been done so far; but even today pathogenesis is obscure and needs to be clarified.

Thus in conclusion, it can be stated that although VX has an otherwise asymptomatic clinical course, yet histopathologically it still poses a challenge to the understanding of its pathogenesis. The two cases presented in this report had varied clinical appearance but very similar and characteristic histopathological presentation to be diagnosed as VX.

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Figures

[Figure 1], [Figure 2], [Figure 3], [Figure 4], [Figure 5]