Case Report

Insight into verruciform xanthoma with oral submucous fibrosis: Case report and review of literature

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Abstract

Verruciform xanthoma (VX) is a rare benign mucocutaneous verrucopapillary lesion, which mainly involves masticatory mucosa and gingiva. Clinically, it presents as a solitary, sessile or pedunculated, white- or yellow-white-colored growth with a pebbled surface, hence often misdiagnosed as papilloma. The hallmark of histological diagnosis is the presence of foam cells or xanthoma cells confined to the connective tissue papillae. We present a case of VX on the maxillary gingiva in a 52-year-old male patient with oral submucous fibrosis (OSF) with a review on histopathology and concomitant oral lesions. The exact etiopathogenesis is not clearly delineated more so when it is associated with diverse local and systemic conditions. Its concomitant association with other conditions such as lichen planus, leukoplakia, oral squamous cell carcinoma and OSF is rare, with only three cases of VX associated with OSF reported earlier.

Keywords: Foam cells, oral submucous fibrosis, verruciform xanthoma

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INTRODUCTION

Verruciform xanthoma (VX) is a rare benign, mucocutaneous, verrucopapillary lesion. It was first described by Shafer in 1971 in the oral cavity, and its occurrence on extraoral sites was first reported by Santa Cruz in 1979.[1] Extraorally, it most commonly occurs on the skin and anogenital mucosa, and intraorally, it predominantly occurs on the masticatory mucosa, with gingiva being the frequent site of occurrence.[2] It clinically appears as a well-demarcated solitary sessile or pedunculated lesion with a rough pebbled surface, yellowish-white or red in appearance depending on the degree of keratinization and the number of lipid-laden macrophages in the connective tissue papilla. VX has been rarely associated with other oral and systemic conditions.[2] Till date, only three cases of VX along with oral submucous fibrosis (OSF) have been reported in the literature by Yu *et al*.,[2] Ghosh *et al*.[3] and Hegde *et al*.[4] Herein, we describe a case of VX associated with OSF, with a review of VX with other oral lesions and etiopathogenesis.

CASE REPORT

A 52-year-old male patient came to the Department of Oral Medicine complaining of a painless growth on the upper anterior gum region since 3 months. Medical, family and drug

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histories were noncontributory, although the patient gave a positive habit history of consuming alcohol 3 times per week and chewing paan-zarda (betel nut + tobacco + slaked lime) 10 times a week. On intraoral examination, a solitary, sessile growth was seen involving the attached gingiva in relation to 13 and 14, extending from the mesial aspect of 13 to the distal aspect of 14. The lesion was yellow-white in color, having a pebbled surface and measuring 0.8 cm × 2.0 cm in size [Figure 1]. Adjacent oral mucosa showed blanching associated with reduced mouth opening (interincisal distance – 35 mm) and reduced tongue protrusion. The bands were palpable on both the sides vertically extending from 26 to 36 [Figure 2]. An intraoral periapical radiograph revealed that the crown and root of the tooth were intact with no periapical involvement and intact interdental bone, indicating that the lesion is of soft tissue origin.

Based on the clinical findings, the case was provisionally diagnosed as verrucous hyperplasia with OSF. A differential diagnosis of VX, papilloma, verrucous carcinoma with OSF was given. An excisional biopsy of the lesion with a surrounding margin of adjacent gingiva was done, and the specimen was sent to the Department of Oral Pathology for further evaluation. On gross examination, the specimen revealed multiple bits of soft tissue measuring 1.0 cm × 2.0 cm in size, having an irregular appearance, grayish-brown in color.

Histopathological evaluation showed epithelial hyperplasia with prominent parakeratinization, and the epithelial ridges were of uniform length [Figure 3]. Within the connective tissue papillae, prominent collections of vacuolated cells with dark basophilic pyknotic nuclei were appreciated suggestive of foam cells or xanthoma cells and were not extending beyond connective tissue papillae [Figure 4]. There was a diffuse dense chronic inflammatory cell infiltrate comprising lymphocytes, macrophages and few plasma cells. The deeper connective tissue showed

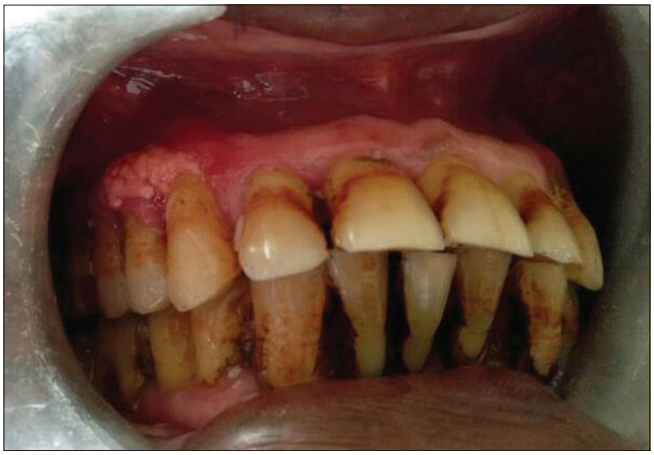

Figure 1: A solitary, sessile lesion with a rough surface and is yellowish-white in color seen on the attached gingiva with respect to 13, 14, 15

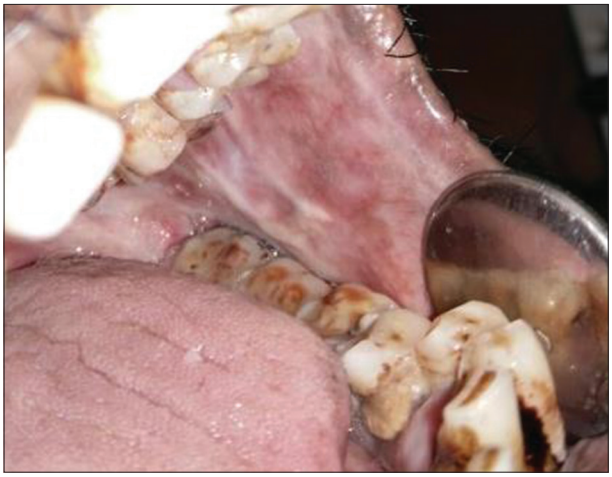

Figure 2: Blanched oral mucosa with reduced mouth opening

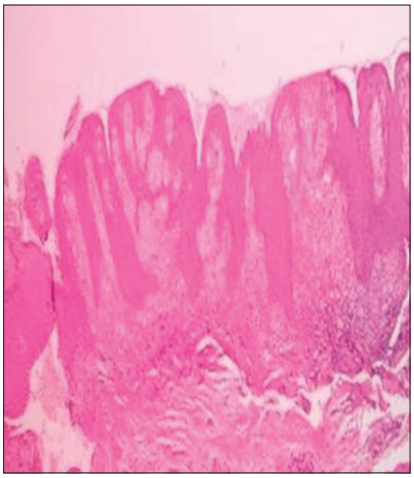

Figure 3: Uniform length of epithelial ridges

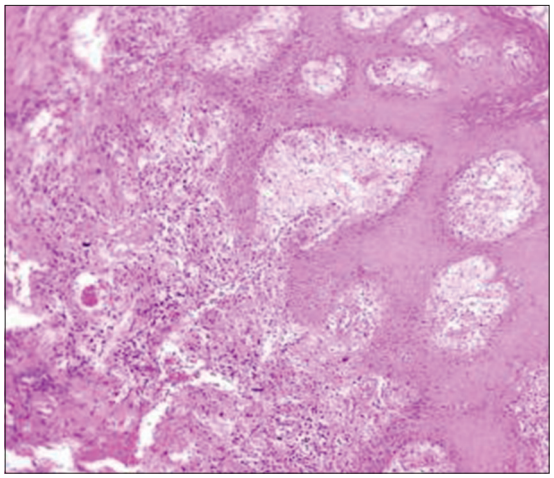

Figure 4: Prominent collections of vacuolated cells with dark basophilic pyknotic nuclei

the presence of thick dense collagen bundles of varying thickness. The adjacent gingiva showed atrophic epithelium with dense eosinophilic hyalinized collagen bundles with dense focal collections of chronic inflammatory cells, and one area showed the presence of sebaceous gland [Figure 5]. On immunohistochemical (IHC) staining with CD68 marker, foam cells showed positivity (+++), indicating a monocyte–macrophage lineage [Figure 6]. A final diagnosis of VX with OSF was given. On follow-up of the patient, the healing of the site was appreciated and the patient is still under review.

DISCUSSION

Xanthoma is derived from the Greek word' Xanthos' which means yellow.[5] These are accumulations of a yellow material containing cholesterol, lipid-laden macrophages and cholesterol esters. They are considered to occur in patients with hypercholesterolemia and with increased levels of low-density lipoprotein whereas xanthoma disseminatum and VX occur in normolipidemic patients.[6]

VX is an uncommon and asymptomatic lesion involving the oral cavity, which most commonly occurs on 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%).[2] It most commonly occurs in the middle age with a mean age of 51 years. There is a slight male predominance to the females in the ratio of 1.1:1 up to the age of 50 years. This ratio is reversed with a slight female predominance with a ratio of 0.8:1 after the age of 50 years. Majority of cases have been described in Caucasians and only few cases reported from India.[1] Most of the lesions are exophytic while some may be crateriform or ulcerated. Its size varies from 0.2 to 2.0 cm, with an exception of a larger lesion reported measuring 4.0 cm × 1.5 cm documented by Graff *et al*.[7]

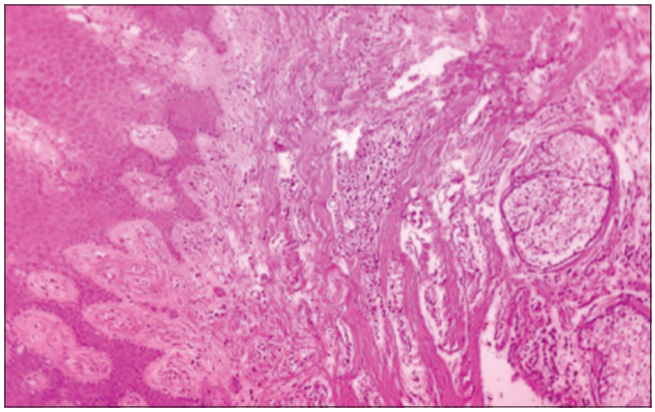

Figure 5: Presence of sebaceous gland

Clinically, it appears as a solitary, sessile or pedunculated lesion with a rough or pebbled, granular or verrucous surface, often misdiagnosed as verrucous carcinoma or papilloma due to its clinical presentation.[1,4] The most common differential diagnosis includes squamous papilloma, verruca vulgaris, verrucous carcinoma and squamous cell carcinoma.[8] However, clinically, majority of squamous papillomas are round in shape with a papillary surface, whitish pedunculated, and verruca vulgaris is firm, circumscribed, elevated with a papillomatous hyperkeratotic surface.[9] Whereas, verrucous carcinomas are large, exophytic–endophytic lesions with a cauliflower surface.[10] Because VX was associated with OSF, which is a potentially malignant disorder, histopathology plays an important role in ruling out underlying dysplasia.

Few dermatology reports have shown a concomitant association of VX with other lesions and systemic conditions such as lichen sclerosis,[11] solar keratoses,[12] CHILD syndrome,[13] lichen planus[14] and graft versus host disease (GVHD)[15]. Oral VX is rarely associated with other oral lesions such as discoid lupus erythematosus,[16] pemphigus vulgaris,[17] lichen planus[14] and GVHDs.[15] The cases have been reported in patients with habits of tobacco and paan, and Neville and Weather reported a case with snuff dipper's keratosis.[18] It is also associated with potentially malignant diseases such as OSF,[2-4] carcinoma *in situ*,[19] erythroplakia[1] and discoid lupus erythematosus (DLE)[16] and two cases of squamous cell carcinoma have been reported by Yu *et al*.[2] and Andrade *et al* [Table 1].[20]

Based on the review of the literature, the total number of cases of VX with OSF reported are 4 including the present case. The first case was reported by Yu *et al*.[2] on the right buccal mucosa in a 28-year-old male patient with a positive

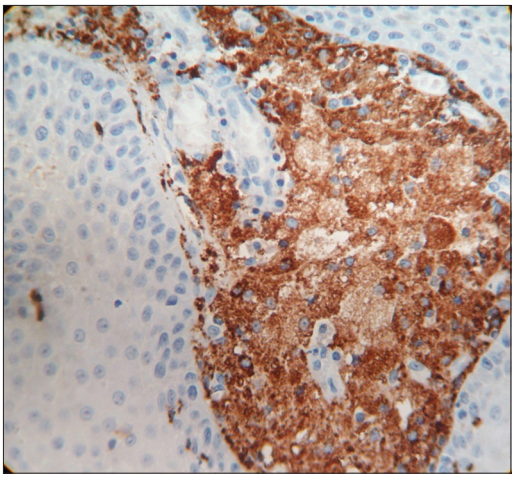

Figure 6: CD68+ showing foam cells in the connective tissue stroma adjacent to the epithelium

Table 1: Case reports of Verruciform Xanthoma and concomitant oral lesions

Condition	Author and years	Gender	Age	Site
Pemphigus vulgaris	Gehrig *et al*. (1983)[17]	Male	15	Tongue
Carcinoma in situ	Drummond *et al*. (1989)[19]	Male	71	A posterior floor of the mouth
Oral lichen planus	Hume *et al*. (1980)[21]	Female	55	Buccal mucosa
	Miyamoto *et al*. (1996)[14]	Female	68	Lateral tongue
	Polonowita *et al*. (1999)[22]	Male	65	Mandibular gingiva
		Female	73	Mandibular alveolar mucosa
		Female	42	Lateral tongue
	Yu *et al*. (2007)[2]	Female	72	Right buccal mucosa
	Stoopler (2012)[23]	NS	NS	NS
	de Andrade *et al*. (2015)[20]	Male	68	Lateral aspect of the tongue
Oral lichen planus with neurofibromatosis	Anbinder *et al*. (2011)[24]	Male	22	Buccal mucosa
Intraoral warty keratosis	Neville and Weathers (1980)[18]	Female	65	Alveolar ridge
Snuff dippers keratosis	Neville and Weathers (1980)[18]	Female	65	Alveolar ridge
Oral graft versus host diseases	Allen and Kapoor (1993)[25]	Male	22	Buccal mucosa
	Sibaud *et al*. (2006)[26]	Male	57	Gingiva
	Shahrabi Farahani *et al*. (2011)[15]	Male	45	Buccal mucosa
		Female	13	Dorsum of tongue
		Male	63	Lateral tongue
		Female	48	Labial mucosa
Graft versus host disease with leukoplakia	Shahrabi Farahani *et al*. (2011)[15]	Male	45	Hard palate
Graft versus host disease associated with erythroplakia	Capocasale *et al*. (2017)[27]	Male	47	Hard palate
Bone marrow transplant with graft versus host disease	Allen and Kapoor (1993)[25]	Male	40	Gingiva
	Xue *et al*. (2016)[28]	Male	22	Lower lip
Oral submucous fibrosis	Yu *et al*. (2007)[2]	Male	28	Right buccal mucosa
	Ghosh *et al*. (2014)[3]	Male	25	Right buccal mucosa
	Hegde U *et al*. (2015)[4]	Male	39	Left buccal mucosa
	Present case	Male	52	Attached gingiva
Oral discoid lupus erythematosus	Poulopoulos *et al*. (2007)[29]	Female	51	Alveolar mucosa
Squamous cell carcinoma	Yu *et al*. (2007)[2]	Male	56	Right ventral surface of tongue
	de Andrade *et al*. (2015)[20]	NS	NS	NS
Paracoccidioides	de Andrade *et al*. (2015)[20]	NS	NS	NS

NS: Not specified

habit history of alcohol consumption, betel quid chewing and cigarette smoking; the second case was reported by Ghosh *et al*.[3] in which bilateral palpable bands on the right and left buccal mucosa were appreciated along with a yellowish-white nonscrappable patch on the right buccal mucosa in a 25-year-old male patient with a positive habit history of tobacco chewing. The third case was reported by Hegde *et al*.[4] where the growth was sessile, pink and papillary on the left buccal mucosa in a 39-year-old OSF male patient.

To the best of our knowledge, the present case is the fourth case reported on the attached gingiva, in a 52-year-old male patient. The differential diagnosis considered was verrucous hyperplasia as many cases of verrucous hyperplasia are associated with gutka chewing with a high transformation rate for malignancy.[30] The malignant transformation of VX is questionable even though few reports have mentioned oral squamous cell carcinoma. In the present case, the patient had a solitary, sessile lesion on the gingiva associated with OSF and histopathology ruled out any epithelial dysplasia with the presence of prominent foam cells.

The lesion was papillary with prominent parakeratinization, epithelial hyperplasia indicating papillary or cauliflower pattern. IHC showed $CD68^{+}$ foam cells, indicating a monocyte–macrophage lineage. The adjacent tissue revealed an atrophic epithelium with dense collagenized hyalinized connective tissue stroma reminiscent of OSF. The presence of sebaceous glands in the lesion showed $CD68^{-}$ and was thought as an incidental finding in the gingiva. The pathogenesis of VX is still obscure with various theories proposed and more so its association with other lesions. The histogenetic origin of the lipid-laden foam cells was controversial, which are regarded as fibroblasts, melanocytes or macrophages. However, with the advent of molecular markers, it has been proved that they are lipid-laden macrophages derived from monocytic–histiocytic origin with CD68 immunoreactivity.[2] Ultrastructurally, the foam cells are filled with the cytoplasmic inclusion of varying density, which appears to be of lysosomal and nonlysosomal form. The non-lysosomal type constituted electron–lucent droplets without a membrane and others were membrane-bound containing lipid and dense granules.[22] Zagarelli *et al*. have explained the formation of foam/xanthoma cells as a consequence of epithelial entrapment with subsequent degeneration and lipid accumulation.[8,31]

The epithelial hyperplasia is suggested to be a secondary response to the presence of foam cells, which affects the nutrition and metabolism of epithelial cells and also releases certain growth factors responsible for inducing epithelial hyperplasia.[5] Rowden *et al*. opinionated that VX belongs to a new category of "non-X histiocytosis," in which the presence of Langerhans cells suggested an immunological pathogenesis.[32] Ide *et al*. proposed that wet environment , PDL pathogens ,mechanical stimuli ,tobacco ,alcohol,drugs and immune response could be the possible etiological agents.[33] The suggested pathogenesis in associated lesions is altered epithelial turnover, or epithelial desquamation, epithelial damage in lichen planus, GVHD, pemphigus., epidermolysis bullosa 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. In the present case the patho-mechanism is elusive, it might be due to microtrauma or epithelial damage leading to macrophage dependent debris removal and macrophage recruitment leading toVX.[21,33] Treatment is surgical excision of the lesion followed by palliative care for OSF, and the recurrence rate is low with no malignant transformation reported so far.[5]

CONCLUSION

VX is an uncommon lesion and its association with other conditions is extremely rare. Clinically, VX is often misdiagnosed with verrucous carcinoma and papillomas. Malignant risk transformation for VX is rare and non-conclusive. But concomitant occurrence with OSF which is a potentially malignant disorder mandates the importance of a thorough clinical and histopathological examination.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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