DOI: 10.7860/JCDR/2023/67001.18798

Case Report

Dentistry Section

Emphasis on Temporal Association between Oral Verruciform Xanthoma and Candidal Infection: A Case Report

RESHMA POOTHAKULATH KRISHNAN[1], DEEPAK PANDIAR[2]

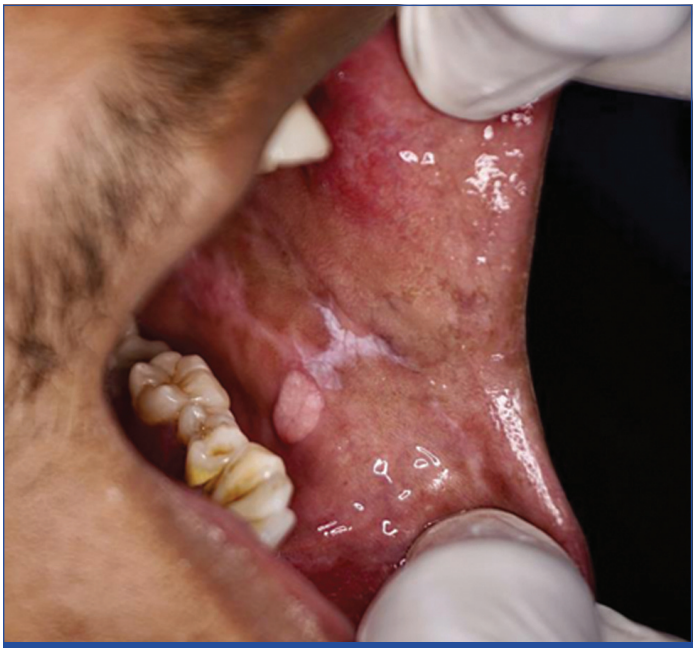
ABSTRACT

Oral Verruciform Xanthoma (VX) is a verrucopapillary lesion seen as a cauliflower-like/papillary growth in the oral cavity. The aetiopathophysiology of VX is explained by several pathogenic processes. The presence of xanthoma cells or foamy macrophages is considered a characteristic feature of this lesion however there is disagreement about the origin of these cells. In this case report, the authors described a case of VX with concomitant candidal infection in a 31 years old male patient. Although not fully explored, a hypothesis is constructed to understand the relationship between *Candida albicans* and VX, combining the current literature and present findings. Presumably, an initiation event varies from patient to patient and site to site, additionally, the candidal infection may also play an important role in the pathogenesis of VX.

Keywords: Candidiasis, Foam cells, Lipid-laden macrophages, Pathogenesis, Pyroptosis

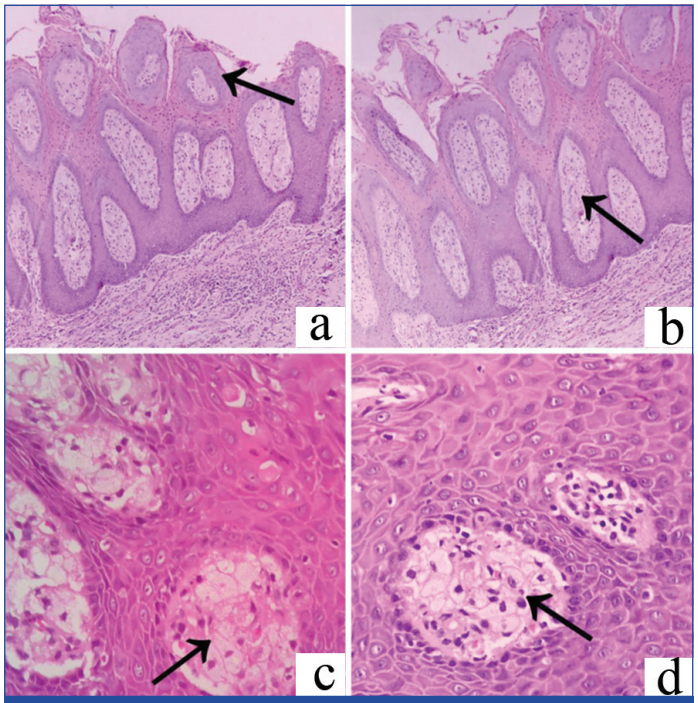
CASE REPORT

A 31 years old, Dravidian male patient reported to the Department of Oral Medicine and Radiology with a complaint of growth and whitish discoloration in his left cheek region for two months. The patient gave history of smoking (1 pack year) and alcohol consumption for the past 10 years. He provided no history of any trauma and was not under any medication. On examination, a papillomatous growth and a greyish-white patch were noted on the left buccal mucosa, measuring 1×1.5 cm and 1.6×0.8 cm, respectively [Table/Fig-1]. The clinical differential diagnosis of non-homogenous leukoplakia, benign papillary lesion, and candidiasis was given.



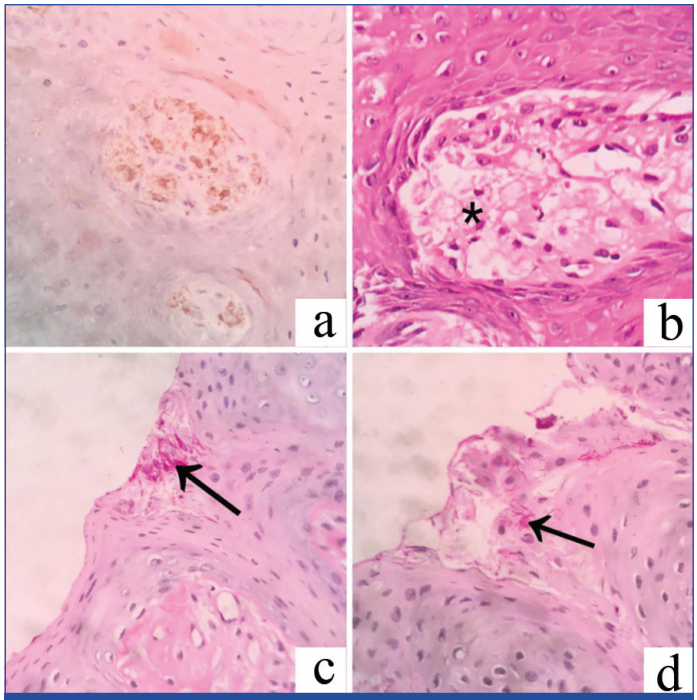
[Table/Fig-1]: Clinical presentation of the lesion.

The growth was surgically excised. Histopathological examination showed hyperparakeratinised stratified squamous epithelium of variable thickness, showing exophytic projections supported by fibrovascular core [Table/Fig-2a,b]. In few areas, the epithelium showed acanthosis and broad rete ridges. There was also evidence of large cells with foamy cytoplasm resembling macrophages confined to the connective tissue papilla between the epithelial rete ridges, not extending into the underlying connective tissue stroma [Table/Fig-2c,d]. Foamy cells were positive to CD-68 [Table/Fig-3a] and negative for S100 antibody. Periodic acid schiff-positive granules were found within the cytoplasm of xanthoma cells.



[Table/Fig-2]: Photomicrograph of H&E stained section showing hyperparakeratinised stratified squamous epithelium with exophytic surface projections supported by fibrovascular core (a-b, 40X) and foamy macrophages between the rete ridges (c-d, 400X).

On careful examination, most of the xanthoma cells present in the fibrovascular core showed signs of rupture [Table/Fig-3b] and candidal hyphae were found in the parakeratin of the epithelium [Table/Fig-3c,d]. Based on the histological and histochemical examination, a final diagnosis of VX with concomitant candidal infection was made. There was no sign of recurrence in the recent follow-up, two years after the excision.



[Table/Fig-3]: Photomicrograph of CD68 positive cells (a, 400X), H&E stained section showing xanthoma cells with signs of rupture (b, 400X) and PAS stained section showing candidal hyphae (c-d, 400X).

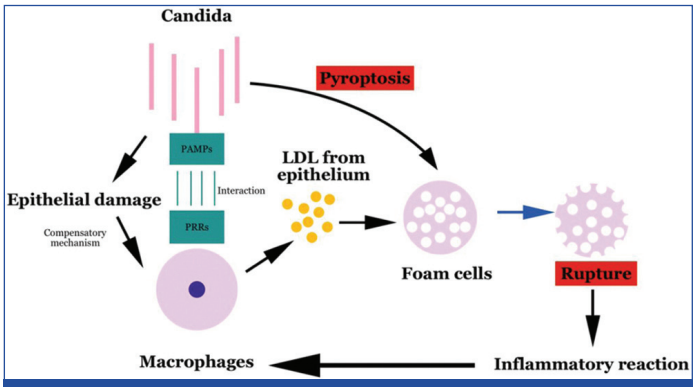
DISCUSSION

The VX is a benign, verrucopapillary lesion seen mainly in the oral cavity [1]. These rare lesions account for approximately 0.025-0.05% of the lesions submitted for histopathological examination [1]. Gingival marginal mucosa, followed by the hard palate are the common sites [2]. Foamy histiocytes/xanthoma cells in histopathological examination are important diagnostic clues for the diagnosis of this lesion. However, the exact pathophysiology and its origin is unknown.

Several plausible theories are explained by different authors in the literature to explain the pathogenesis of VX. Local trauma, alcohol and tobacco intake, inflammatory agents, pathogens, immunological diseases, and pathologies like carcinoma in situ that alter the turnover of epithelial cells are all considered possible agents for the initiation of this rare lesion [3,4]. In the present case, the patient had history of smoking and alcohol consumption for the past 10 years and candidal hyphae were evident in the superficial parakeratotic layers. It is not known whether the VX was related to candida albicans in this patient, however, the association between these two lesions at the same site is interesting. In this article, a hypothesis is constructed to explain the relationship between VX and *Candida albicans*.

Macrophages, known to be antigen-presenting cells, migrate towards the epithelium colonised by candida as a compensatory phenomenon. Macrophages recognise candida through PRRs (pattern recognition receptors), which interact with specific molecules called Pathogen-Associated Molecular Patterns (PAMPS) exposed on the surface of Candida [5]. It may also be possible that *Candida albicans* leads to epithelial damage which further recruits macrophages and lymphocytes in VX. Tabata T et al., reported that chronic inflammation activates T-lymphocytes and recruits macrophages with CCR2 (C-C chemokine receptor type 2) protein [6]. This immunological activity upregulates Macrophage Scavenger Receptor (MSR) on the macrophages and traps lipoproteins (especially low-density lipoproteins) from the epithelial cells [6,7]. These then oxidise to form foam cells [7]. The macrophages express Ox (oxidised)- LDL and MSR-1. MSR-1 is important for the self-sustenance of the lesion and Ox-LDL is a chemo-attractant for T lymphocytes and foam cells [6]. This explains the presence of macrophages and lymphocytes in the present case as well as other VX cases. Alcohol and tobacco consumption, along with the superficial candida infection can be the cause of chronic inflammation in this patient. The superficial keratinocytes exhibiting highly eosinophilic cytoplasm with small intracytoplasmic vacuoles and pyknotic central nuclei like in this case the mechanism of epithelial degeneration was further supported.

In the present case, most of the xanthoma cells in the fibrovascular core showed signs of rupture [Table/Fig-3b]. It has been reported that the fungal pathogen, *Candida albicans* causes macrophage death by various mechanisms [8]. During phagocytosis, *C.albicans* triggers pyroptosis, a programmed death [8]. Pyroptosis is a type of highly inflammatory lytic form of cell death triggered usually by microbial agents [9]. Ide F et al., in their ultrastructural analysis reported that the foam cells showed features of necrosis, including rupture of the cell membrane [3]. This results in increased local macrophage trafficking [3]. Altogether, the *candida albicans* initiate and cause rupture of the foam cells present in VX, and these macrophages further cause local macrophage trafficking. This produces a viscous loop for the persistence of the VX. The plausible association between VX and candidal infection is represented in [Table/Fig-4]. It is important to emphasise that the clinical presentation of oral VX is not very specific [10,11]. The verrucous or papillary appearance of the lesion with a pedunculated or broad base often leads to a clinical misdiagnosis of squamous cell carcinoma, papilloma, verrucous hyperplasia, or verrucous carcinoma [12,13].



[Table/Fig-4]: Plausible association between Verruciform Xanthoma (VX) and candidal infection.

Although malignant transformation of VX is not reported in the literature, there are reported cases of VX associated with squamous cell carcinoma and carcinoma in situ [14,15]. Hence, a careful surgical excision of the lesion with sufficient marginal clearance is advised.

CONCLUSION(S)

The initiation event varies from patient to patient and VX must be differentiated from various hyperplastic lesions of the oral cavity. Tobacco, alcohol, drugs, sensitising or allergic agents, and pathogens, including *candida albicans*, play an important role in the initiation of oral VX.

REFERENCES

[1] Belknap AN, Islam MN, Bhattacharyya I, Cohen DM, Fitzpatrick SG. Oral verruciform xanthoma: A series of 212 cases and review of the literature. Head Neck Pathol. 2020;14(3):742-48.
[2] Hwang MJ, Yu-Fong Chang J, Chiang CP, Jin YT. Oral verruciform xanthoma: Case report. J Dent Sci. 2023;18(2):936-38.
[3] Ide F, Obara K, Yamada H, Mishima K, Saito I, Kusama K. Cellular basis of verruciform xanthoma: Immunohistochemical and ultrastructural characterization. Oral Dis. 2008;14(2):150-57.
[4] Javadi T, Saeed F, Parker DC, Magliocca KR. Verruciform xanthoma: Clinical and morphologic spectrum across oral, genital, and cutaneous sites. Head Neck Pathol. 2023;17(3):673-78.
[5] Mukhopadhyay S, Herre J, Brown GD, Gordon S. The potential for Toll-like receptors to collaborate with other innate immune receptors. Immunology. 2004;112(4):521-30.
[6] Tabata T, Mine S, Kawahara C, Okada Y, Tanaka Y. Monocyte chemoattractant protein-1 induces scavenger receptor expression and monocyte differentiation into foam cells. Biochem Biophys Res Commun. 2003;305(2):380-85.

[7] Gruber EJ, Aygun AY, Leifer CA. Macrophage uptake of oxidised and acetylated low-density lipoproteins and generation of reactive oxygen species are regulated by linear stiffness of the growth surface. PLoS One. 2021;16(12):e0260756.
[8] Briard B, Malireddi RKS, Kanneganti TD. Role of inflammasomes/pyroptosis and PANoptosis during fungal infection. PLoS Pathog. 2021;17(3):e1009358.
[9] Tan Y, Chen Q, Li X, Zeng Z, Xiong W, Li G, et al. Pyroptosis: A new paradigm of cell death for fighting against cancer. J Exp Clin Cancer Res. 2021;40(1):153.
[10] Battistelli LS, Américo MG, Gonçalves ABS, Anbinder AL. Oral Verruciform xanthoma: Report of two cases. Med Oral Patol Oral Cir Bucal. 2018;23(4):e429-35.
[11] Hegde U, Doddawad VG, Sreeshyla H, Patil R. Verruciform xanthoma: A view on the concepts of its aetiopathogenesis. J Oral Maxillofac Pathol. 2013;17(3):392-96.
[12] Jain A, Aseervatham Selvi SJ, Arumugam P, Jayaseelan VP. A computational approach to identify the mutations in the genes of the RTK signaling pathway and their possible association with oral squamous cell carcinoma. Middle East J Cancer. 2021;12(1):01-09.
[13] Abijeth B, Ezhilarasan D. Syringic acid induces apoptosis in human oral squamous carcinoma cells through mitochondrial pathway. J Oral Maxillofac Pathol. 2020;24(1):40-45.
[14] Mannes KD, Dekle CL, Requena L, Sangueza OP. Verruciform xanthoma associated with squamous cell carcinoma. Am J Dermatopathol. 1999;21(1):66-69.
[15] Drummond JF, White DK, Damm DD, Cramer JR. Verruciform xanthoma within carcinoma in situ. J Oral Maxillofac Surg. 1989;47(4):398-400.

PARTICULARS OF CONTRIBUTORS:
1. Senior Lecturer, Department of Oral Pathology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India.
2. Reader, Department of Oral Pathology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Reshma Poothakulath Krishnan,
Senior Lecturer, Department of Oral Pathology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai-600077, Tamil Nadu, India.
E-mail: reshmakpai@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 13, 2023
- Manual Googling: Nov 01, 2023
- iThenticate Software: Nov 04, 2023 (14%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Aug 12, 2023**
Date of Peer Review: **Oct 14, 2023**
Date of Acceptance: **Nov 06, 2023**
Date of Publishing: **Dec 01, 2023**