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Verruciform xanthoma and concomitant lichen planus of the oral mucosa.

A report of three cases

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Abstract. Verruciform xanthomas are benign muco-cutaneous lesions of unknown aetiology. They have a papillated surface and histologically they are characterised by the presence of foam cells in connective tissue papillae between elongated parakeratinised epithelial rete ridges. Three cases are reported in which oral mucosal verruciform xanthoma and oral mucosal lichen planus occurred concomitantly.

Key words: verruciform xanthoma; lichen planus; oral mucosa; oral pathology.

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Verruciform xanthomas (VX's) are benign lesions which were first described by SHAFER in 1971[17]. Most cases occur on the oral mucosa, although there are infrequent reports of their development at other mucosal and skin sites[13,16,19]. The lesions are usually asymptomatic, solitary, slow-growing yellowish lesions with a slightly elevated, papillary surface[13,14,17]. They rarely reach more than 1 cm in diameter. Intra-oral sites of predilection are the gingivae and alveolar ridges[13,14]. There is no marked gender predilection[13,14]. VX can have the clinical appearance of a papilloma, verruca, verrucous carcinoma or squamous cell carcinoma.

The diagnosis is made on the basis of the histological appearance with hyperplastic parakeratinised stratified squamous epithelium, showing characteristic elongated thin anastomosing rete ridges extending to a uniform depth into the connective tissue. The connective tissue papillae contain numerous engorged foam cells with an underlying mixed chronic inflammatory cell infiltrate[13,17]. Excision is usually curative[17].

VX's have been reported in association with other conditions including discoid lupus erythematosus[10], pemphigus vulgaris[6], epidermal dysplasia[9], bone marrow transplantation[1], and a syndrome of congenital hemidysplasia with ichthyosiform erythroderma and limb defects[21]. MIYAMOTO et al.[11] reported one case of VX occurring in conjunction with oral mucosal lichen planus (OMLP).

Three cases of oral mucosal VX that occurred concomitantly in patients with oral mucosal lichen planus lesions are presented.

Case reports

Case 1

A 65-year-old Vietnamese man was referred to the Oral Medicine Clinic at the Royal Dental Hospital of Melbourne for assessment of bilateral white patches on his cheek mucosa (Fig. 1a). His medical history was unremarkable and he was not taking any medication. He had smoked up to 30 self-rolled, unfiltered tobacco cigarettes a day, but, one year prior to presenting, had reduced his smoking to 10 cigarettes a day. His alcohol intake was reduced at the same time from approximately 40 g of beer a day to 80 g per week. An incisional biopsy was taken of the white lesion in his right cheek mucosa. Haematoxylin and eosin (H&E) stained slides showed basal epithelial cell lysis, the ingress of inflammatory cells into the lower aspects of the epithelium, and a well-defined band-like infiltrate of chronic inflammatory cells, predominantly lymphocytes, in the superficial connective tissue (Fig. 1b). Direct immunofluorescence showed fibrillar staining at the basement membrane zone with anti-fibrinogen. It was considered that these findings fulfilled the criteria for the diagnosis of OMLP[3,4]. The lesions were asymptomatic and no medication was prescribed. He was reviewed at three-monthly intervals.

There was no change until nine months after the initial presentation, when an exophytic papillary white lesion was noted in the gingival tissues associated with the periodontally-involved lower right second molar tooth (Fig. 1c). The tooth was extracted and an incisional biopsy was taken from the soft tissue. A diagnosis of VX was made using the accepted histopathological criteria[3]. The

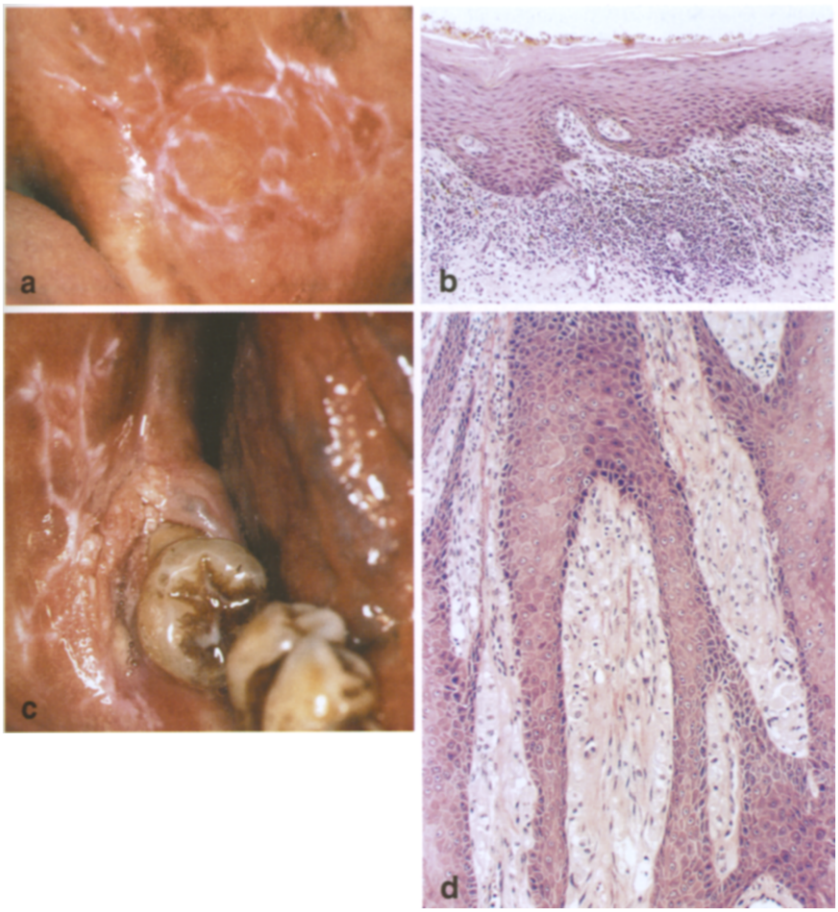
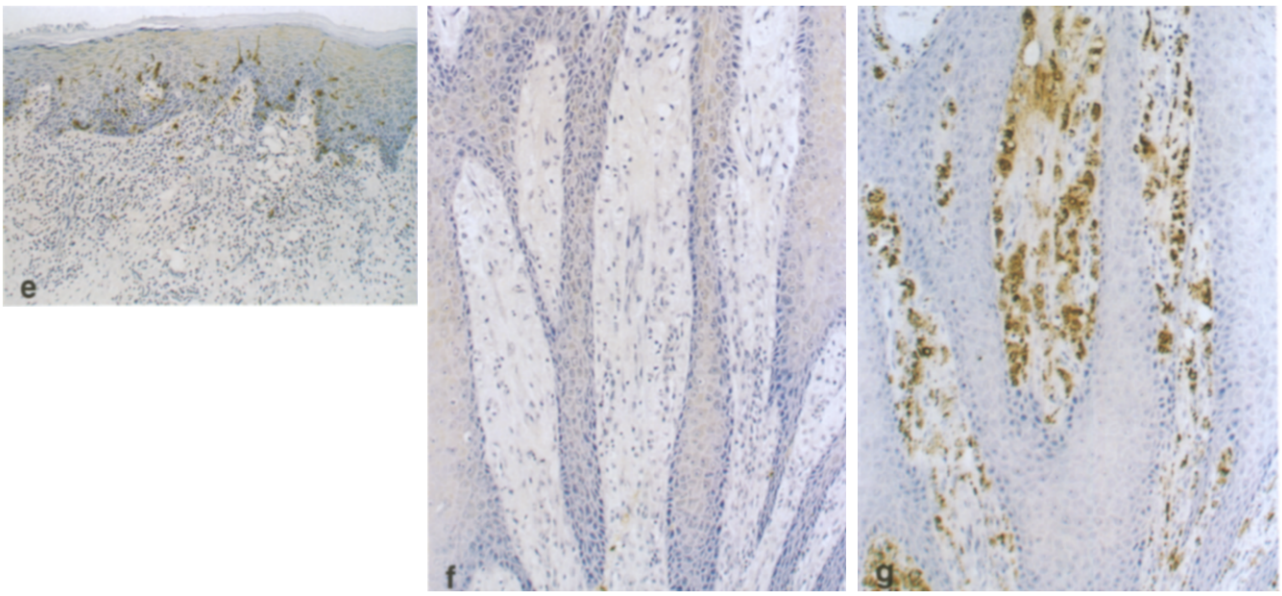


Fig. 1a. Clinical photograph of left cheek mucosa of Case 1 at time of presentation with bilateral white lesions on cheek mucosa. *Fig. 1b.* Photomicrograph from biopsy of buccal mucosa shown in Fig. 1a (H&E ×10). A histological diagnosis of OMLP was made. *Fig. 1c.* Clinical photograph of exophytic papillary lesion associated with periodontally-involved 47 in Case 1, nine months after initial presentation. *Fig. 1d.* Photomicrograph from biopsy of soft tissue shown in Fig. 1c (H&E ×10). Engorged "foam cells" are present between elongated rete ridges, typical of VX. *Fig. 1e.* Photomicrograph showing numerous S-100 +ve dendritic cells in epithelium adjacent to VX in Case 1 (S-100 [Dako, Glostrup, Denmark] ×10; formalin-fixed paraffin-embedded [FFPE] tissue, routine avidin-biotin complex [ABC] technique). *Fig. 1f.* Photomicrograph showing few S-100 +ve dendritic cells in epithelium of VX in Case 1 (S-100 ×10; FFPE tissue, routine ABC technique). *Fig. 1g.* Photomicrograph showing CD68+ve xanthoma cells in connective tissue of VX in Case 1 (CD68 PG-M1 [Dako, Glostrup, Denmark] ×10; FFPE tissue, routine ABC technique).



histopathological characteristics of the lesion are illustrated in Fig. 1d.

The exophytic lesion persisted adjacent to the tooth socket and was excised approximately six weeks after the incisional biopsy. The histological features were unchanged from the incisional procedure. Review over the next 18 months showed reticular white patches on the right and left cheek mucosa with no evidence of recurrence of VX.

Formalin-fixed paraffin-embedded material from the specimens was processed for immunohistochemical evaluation with S-100 and macrophage CD68 PG-M1 antibodies (Dako, Glostrup, Denmark) using a routine avidin-biotin complex technique. S-100 positive dendritic cells were present in the lower half of the epithelium of the OMLP biopsy, with a few positive cells in the sub-epithelial inflammatory infiltrate. The number of positive cells was assessed in a semi-quantitative

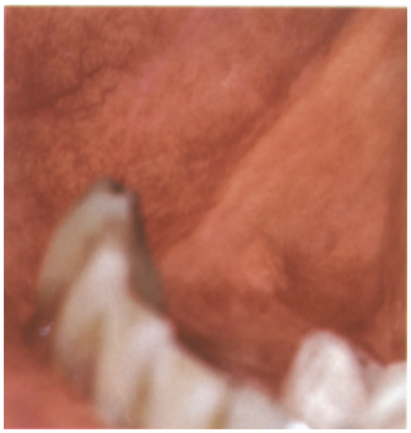


Fig. 2. Clinical photograph of right cheek mucosa and alveolar mucosa of Case 2 showing faint white striae and raised papillary lesion.

manner (Table 1). CD68 positive cells were also seen in the inflammatory infiltrate. S-100 positive dendritic cells were present in the epithelium adjacent to the VX (Fig. 1e), but were markedly reduced in number in the lesional epithelium (Fig. 1f). The xanthoma cells were strongly CD68 positive (Fig. 1g). Periodic acid Schiff (PAS) stained slides showed no evidence of *Candida*.

Case 2

A 73-year-old white woman was referred to the Oral Medicine Clinic at The Royal Dental Hospital of Melbourne for assessment of white patches on the cheek mucosa. She had no relevant medical history and was taking no medication. Examination showed white striae on the right cheek mucosa and a verruciform lesion on the right edentulous lingual alveolar mucosa in the region of the mandibular second molar tooth (Fig. 2). An incisional biopsy was taken from the cheek mucosa showing white striae, and the verruciform lesion was excised. The diagnoses of OMLP and VX were established using the accepted criteria[3,4].

The histological and immunohistochemical findings were the same as those for Case 1 (Table 1).

Case 3

A 42-year-old white woman attended her dental practitioner for assessment of oral mucosal discomfort. White plaques and striae were observed on the cheek and tongue mucosae, as well as a whitish raised papillary lesion on the right anterior lateral margin of her tongue. She had no relevant medical history and was on no regular medication. An incisional biopsy was taken from the right cheek mucosa, and the lesion on the right lateral margin of the tongue was excised. Both specimens were submitted to the Oral Pathology Diagnostic Service at the University of Melbourne, where diagnoses of OMLP (cheek mucosa) and VX (tongue mucosa) were made using the accepted criteria[3,4]. The immunohistochemical findings were the same as those for Cases 1 and 2 (Table 1; Figs. 3a, 3b, 3c).

Discussion

The aetiology and pathogenesis of VX is uncertain. Whilst there is a report of multiple VX's developing in a child with a lipid storage disease[20], it is not usually associated with a systemic abnormality of lipid metabolism[13,20]. Infection with human papillomavirus (HPV) is an unlikely cause, since HELM et al.[7] found that *in situ* hybridization for HPV types 6/11, 16/18 and 31,33 was negative in a VX on the skin of an immunocom-

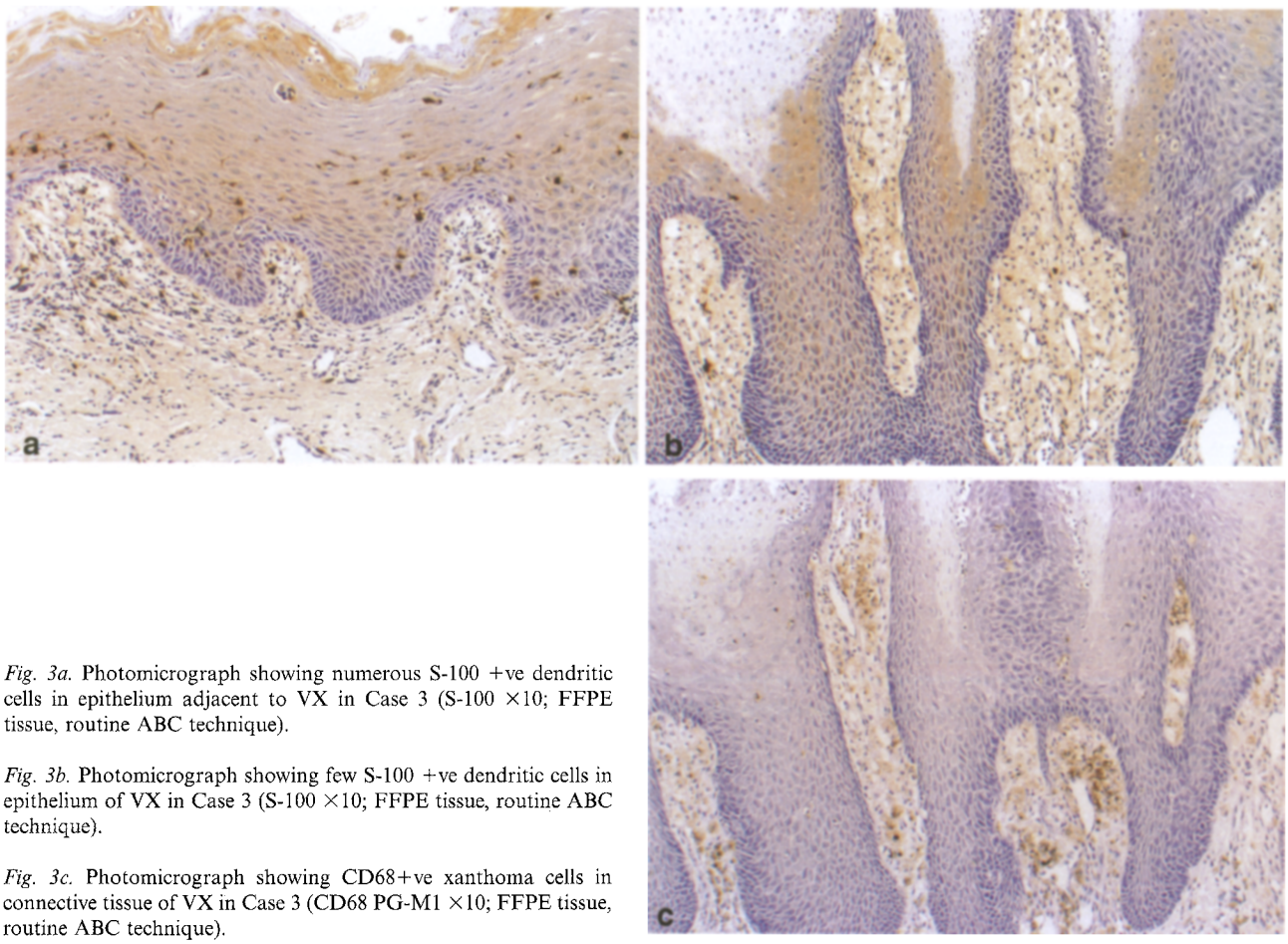


Fig. 3a. Photomicrograph showing numerous S-100 +ve dendritic cells in epithelium adjacent to VX in Case 3 (S-100 ×10; FFPE tissue, routine ABC technique).

Fig. 3b. Photomicrograph showing few S-100 +ve dendritic cells in epithelium of VX in Case 3 (S-100 ×10; FFPE tissue, routine ABC technique).

Fig. 3c. Photomicrograph showing CD68+ve xanthoma cells in connective tissue of VX in Case 3 (CD68 PG-M1 ×10; FFPE tissue, routine ABC technique).

Table 1. Immunohistochemical staining of VX

	Specific staining for S100	Specific staining for CD68
CASE 1	**Epithelium** perilesional +++ lesional − **Connective Tissue** xanthoma cells − inflammatory infiltrate +	**Epithelium** perilesional − lesional + **Connective Tissue** xanthoma cells +++ inflammatory infiltrate ++
CASE 2	**Epithelium** perilesional ++ lesional − **Connective Tissue** xanthoma cells − inflammatory infiltrate +	**Epithelium** perilesional − lesional + **Connective Tissue** xanthoma cells +++ inflammatory infiltrate +
CASE 3	**Epithelium** perilesional +++ lesional + **Connective Tissue** xanthoma cells − inflammatory infiltrate ++	**Epithelium** perilesional − lesional + **Connective Tissue** xanthoma cells +++ inflammatory infiltrate ++

− no staining, + occasional positive cells, ++ moderate numbers of positive cells, +++ large numbers of positive cells.

promised female, and IAMAROON & VICKERS[8] found that 11/12 intra-oral VX's were negative for HPV types 6/11. The presence of candidal hyphae in the superficial parakeratotic layers has been noted in some cases[13]. This is likely to be a secondary infection and there was no evidence of *Candida* in the present cases. Trauma resulting in epithelial cell degeneration, with the cells later phagocytosed by macrophages, has been suggested[22], as has a localised cell-mediated immunological disorder[12].

There is little doubt that the xanthoma cells in VX are of macrophage/monocyte lineage, as demonstrated by positive staining with macrophage markers and negative S-100 staining[5,12,15,18]. The results from the present study were in accord with these findings. Many of the CD68 positive xanthoma cells have been shown to co-express scavenger receptors[5]. The presence of small numbers of CD68 positive cells in the epithelium of VX's noted in the present study and the concentration of CD68 positive xanthoma cells in the superficial connective tissue adds weight to the proposition that the source of the phagocytosed lipid is from keratinocytes[2].

An interesting finding in the current study was a marked decrease in the number of S-100 positive dendritic cells (Langerhans' cells and melanocytes) in the epithelium of the VX in comparison with the adjacent epithelium, as has been previously reported in one case of cutaneous VX[5]. This observation led to the proposition that reciprocal regulatory mechanisms may exist between the Langerhans' cells and xanthoma cells in VX[5].

We suggest that the pathological processes associated with lichen planus is one situation in which the perturbation of epithelium allows for phagocytosis of keratinocyte lipid by macrophages. This process is clearly not specific to lichen planus and, hence, we believe that the rare lesion VX and the common lesion OMLP, or other inflammatory disorders, may occur concomitantly without there being a specific causal relationship between VX and OMLP.

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