REVIEW ARTICLE

Verruciform xanthoma: A view on the concepts of its etiopathogenesis

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ABSTRACT

Verruciform xanthoma is a very uncommon papillary growth seen chiefly in the oral mucosa. The presence of foam cells in the connective tissue papillae between the epithelial rete ridges forms the hallmark in its diagnosis. There has been wide speculation and various hypotheses put forth in explaining the etiopathogenesis of verruciform xanthoma and the origin of foam cells. This article aims to update the different hypotheses in understanding the pathogenesis of the lesion.

Key words: Foam cells, verruciform xanthoma, papillary growth

INTRODUCTION

Verruciform xanthoma is a papillary or cauliflower-like growth seen chiefly in the oral mucosa. It was first described by Shafer in 1971.[1] It is an uncommon lesion with an incidence rate of 0.025-0.05% of all the pathology cases and hence are usually diagnosed clinically as papillomas. However, the histopathological findings are diagnostic of these lesions. Very few cases of verruciform xanthoma occurring extraorally have been reported. The extraoral lesions are usually associated with other conditions such as lymphedema, epidermal nevi and Congenital Hemidysplasia with Ichthyosiform erythroderma and Limb Defects (CHILD) syndrome.[2]

Although, the presence of foamy histiocytes within the elongated dermal papillae forms the hallmark of histopathologic diagnosis of verruciform xanthoma, the nature and origin of these foam/xanthoma cells are debatable even today.

Various pathogenic mechanisms are put forth to explain the presence of xanthoma cells in verruciform xanthoma. The latest concept in its etiopathogenesis is an immune mechanism to local trauma or inflammation. The immunohistochemical studies have shown that the predominant cells in the inflammatory infiltrate are T cells.[3] The foam cells are thought to be of monocyte/macrophage lineage, since they are positive to CD68 antibody (a macrophage marker).[4]

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CLINICAL FEATURES

Verruciform xanthoma is a relatively uncommon hyperplastic condition of the epithelium affecting primarily the oral mucosa.[2] Extraoral verruciform xanthoma was first described on vulva by Santa Cruz and Martin. The extraoral occurrence has been reported mainly involving the anogenital mucosa and skin.[5]

Gingiva, alveolar mucosa and hard palate are the most common intraoral sites of its occurrence.[5] It usually presents as a solitary, sessile or pedunculated lesion with rough or pebbly surface. It is generally asymptomatic and is about 2 mm-1.5 cm in size with a normal/pale/white/red color. It is reported to occur in adults between 40 and 70 years.[2] The review by Philipsen *et al*., has suggested that oral verruciform xanthomas are common in males below the age of 50 years and a reverse trend was noted in females where the lesion was noted in age group above 50 years.[5]

Verruciform xanthoma occurs as an isolated solitary lesion in most cases. But multiple lesions and its association with other diseases such as snuff dipper's keratosis, oral pemphigus vulgaris, carcinoma *in situ*, lichen sclerosus, solar keratoses, discoid lupus erythematosus, epithelial nevus, CHILD syndrome,[6] regressive dystrophic epidermolysis bullosa,[7] seborrheic keratosis[8] and psoriasis[9] have been reported.

It has also been reported in an immunocompromised patient,[10] in patients with hypercholestrolemia and hepatitis C virus carriers.[11] Concomitantly verruciform xanthoma has been

reported with other oral mucosal diseases such as lichen planus, leukoplakia and amyloidosis.[11] Only one report of its association with systemic lipid storage disease has been reported. Hence, it does not seem to be related to any lipid metabolism abnormality.[6]

ETIOPATHOGENESIS

Lot of views exists regarding the etiopathogenesis of verruciform xanthoma. With the advent of immunohistochemistry the definite origin of the characteristic foam cells in this lesion has been possible. Few studies have further indicated the nature of these xanthoma cells and thus attempted to characterize the phenotype of these cells. This has further helped us in understanding the etiopathogenesis of verruciform xanthoma.

Local trauma, inflammation[6] and conditions other than epithelial trauma, which affect the turnover of epithelium such as carcinoma *in situ*, candida infection, a local immunological disorder[12] and also a viral infection[6] have been considered as the different possible etiologic agents in verruciform xanthoma. The ultrastructural and *in situ* hybridization findings in verruciform xanthoma, disclosed negativity for the HPV in these lesions. Hence, the viral etiology has not gained much impetus.[6]

Foam cells

The foam cells are large cells with foamy cytoplasm, which stain positively with Periodic Acid-Schiff (PAS) and are diastase resistant, implying that the material in the foam cells is not glycogen. The chemical studies by gas chromatography of extracted material have shown a preponderance of cholesterol esters.[2] The ultrastructural findings have suggested that the foam cells are fat laden macrophages with lipid content.[2]

The extensive immunohistochemical studies by Mostafa *et al*., have suggested that the foam cells of verruciform xanthoma are of monocyte-macrophage lineage since there was intense cytoplasmic positivity for anti-CD68 monoclonal antibodies.[12] This finding has been subsequently confirmed by other independent studies.[9] Apart from positivity of foam cells to anti-CD68 antibodies, these cells have also been reported to stain positively for cathepsin B, another macrophage marker. Thus, it is clear that the foam cells are of monocyte macrophage lineage.[9] The negativity of these cells to S-100 ruled out the possibility of the origin of these xanthoma cells from dermal dendritic cells.[13]

The macrophages are known to differ according to their location, morphology and function. In order to understand the nature of these macrophages and identify their subpopulation, Rawal *et al*., have conducted studies using immunohistochemical probes.[9] They found that a majority of foam cells in verruciform xanthoma were of resident mature chronic inflammatory reparative phenotypes, with only a minor population of acute inflammatory subtype. This finding was consistent in various anatomic sites considered such as gingiva, palate and other mucosa. A conclusion that verruciform xanthoma involves chronic inflammatory process where the role of acute inflammatory cells is limited was drawn. This result is consistent with the clinical characteristics of verruciform xanthoma as an asymptomatic and slow growing lesion.[9]

Epithelial hyperplasia

Mostafa *et al*., have suggested that the epithelial hyperplasia in verruciform xanthoma is just an illusion and there is no proliferation of epithelial cells with downward growth of the rete pegs, but rather it is a result of upward pushing effect by accumulated macrophages towards the epithelium. This according to authors also explains the thinning of epithelium overlying the macrophages in the connective tissue papillae.[12] However, Mostafa *et al*., could not demonstrate degenerated epithelial cells either ultrastructurally or immunohistochemically.[13]

Nowparast *et al*., opine that the epithelial hyperplasia and hyperkeratotic change is secondary to the presence of foam cells which affect the nutrition and the metabolism of epithelial cells.[14]

Travis *et al*., also suggested that the epithelial hyperplasia is secondary to the presence of foam cells, which produce a variety of growth factors that might play a role in inducing the hyperplasia.[15]

The hyperplasia of the epithelium is a vicious cycle related to chronic inflammation. T-cells are activated as a result of chronic inflammation and these T-cells in turn release cytokines which bring about the hyperplasia. The hyperplastic epithelium expresses human leukocyte antigen-DR (HLA-DR) and interleukin (IL)-8 molecules.[16,17] The stimulated keratinocytes with HLA-DR molecules in turn release cytokines that increase the T cell trafficking. IL-8 molecules on the other hand bring about HLA-DR + neutrophil exocytosis into parakeratin layer.[18] Together the increased T-cells and neutrophils activate the T-cells to release cytokines that bring about epithelial hyperplasia.[16] Thus the cycle continues.

Source of lipid

It has been reported that the squamous epithelia are active sites of lipid biosynthesis and there is an increase in epidermal lipids in chronic inflammatory dermatoses including verruciform xanthoma.[19] The ultrastructural findings of membrane bound vacuoles in keratinocytes and foamy macrophages in epithelium of verruciform xanthoma further support this.[11]

Keratinocyte-basal lamina complex in verruciform xanthoma

The flattening of the keratinocytes in verruciform xanthoma is believed not to be a mechanical one by the foam cell pool, but rather a result of degeneration and squamatization of the keratinocytes. This is a morphologic sign of chronic epithelial damage, which is also seen in other interface mucodermatoses.[20] The ultrastructural findings of Ide *et al*., also support this.[11] However, the effect of neutrophils on this is said to be minimal or insignificant as similar intraepithelial neutrophil aggregation is present in psoriasis but does not progress to verruciform xanthoma.[20] Also there is scarcity of (growth factor receptor-bound protein) GrB^+ cells in verruciform xanthoma unlike in lichen planus. This implies that the T-cell mediated cytotoxicity plays a significant role in the disruption of the basal lamina and keratinolysis in verruciform xanthoma.[11]

Mechanism of macrophage recruitment in connective tissue papillae

Monocyte chemotactic protein-1 (MCP-1), a potent monocyte/macrophage attractor has been localized in the basal cells of verruciform xanthoma[18] and its shared receptor chemokine (C-C motif) ligand 2 (CCR2) on the macrophages. The activated T-cells are known to modulate the production of these ligand-receptor pair (MCP-1 and CCR2), which upregulates the macrophage and T-cell trafficking into the sub-basal papillae. Both MCP-1 and CCR2 are expressed in the foam cells of verruciform xanthoma. Similar mechanism has been reported in chronic inflammatory diseases in adults, in gingivitis and periodontitis.[17,18,21]

Transformation of macrophages to foam cells

The activated T-lymphocytes due to chronic inflammation recruit macrophages with CCR2 molecules, which in turn upregulates the expression of macrophage scavenger receptor (MSR) on them.[22] These macrophages recognize, trap and internalize the low density lipoproteins (LDL) from the epithelial cells and oxidize it resulting in foam cells.[23] The foam cells express MSR-1 and Ox (oxidized)-LDL. MSR-1 helps in self-sustenance of the long lasting verruciform xanthoma and Ox-LDL acts as a chemoattractant for macrophages and T-cells.[22,24]

According to Zegarelli *et al*., inflammation due to local irritant or trauma initiates the development of verruciform xanthoma[25] [Figure 1].

Earlier in 1986, Rowden *et al*., suggested an immunological pathogenesis because of the presence of the Langerhans cells.[13] But, subsequent studies have documented scarcity of these cells in verruciform xanthoma.[9] Though Mostafa *et al*., could not determine exactly the cause or mechanism of immune reaction, they suggested cell-mediated local immune reaction as the probable underlying mechanism in verruciform xanthoma, since the predominant infiltrated lymphocytes in verruciform xanthoma lesions were identified as T cell type by them.[12] T-lymphocytes are very well known to produce lymphocyte mediator which lead to their accumulation at the site of antigen, thus explaining their presence.[9]

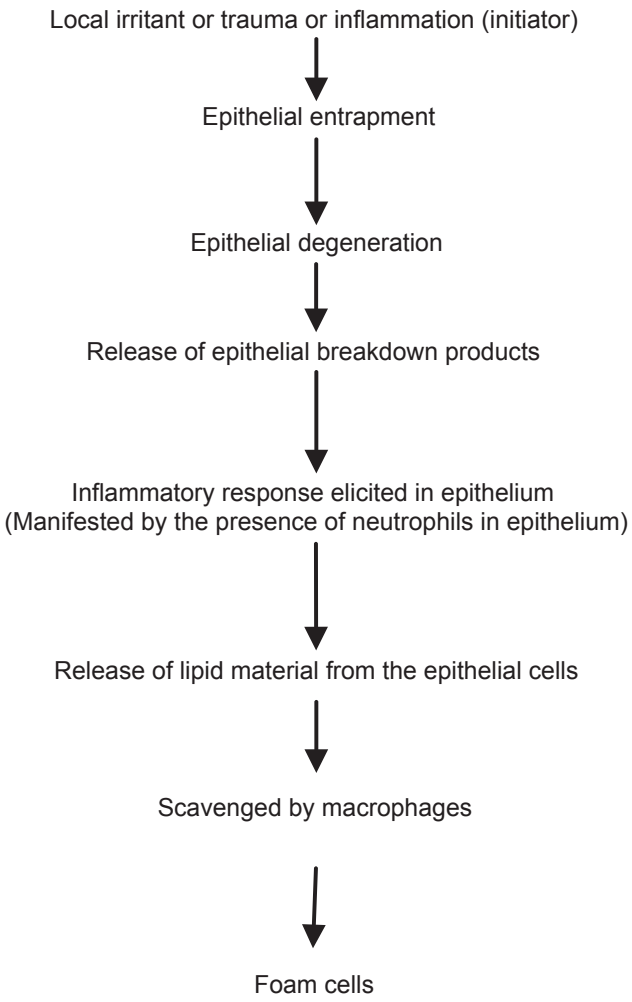

Figure 1: Flowchart showing etiopathogenesis of verruciform xanthoma

Even an immunologic response similar to that of lichen planus has been suggested to explain the pathogenesis of verruciform xanthoma.[6] It is said that memory T-lymphocyte binds with bacteria or food antigens in low affinity cross-reaction without threshold for cell activation and proliferation, which explains the uncommon occurrence of the lesion.[9] In few cutaneous verruciform xanthoma, mutation of 3β-hydroxyl steroid dehydrogenase was noted, suggesting a genetic etiology.[9]

The different hypotheses of the immunopathogenesis of verruciform xanthoma based on various findings are explained in Figure 2.[11,13,17-24]

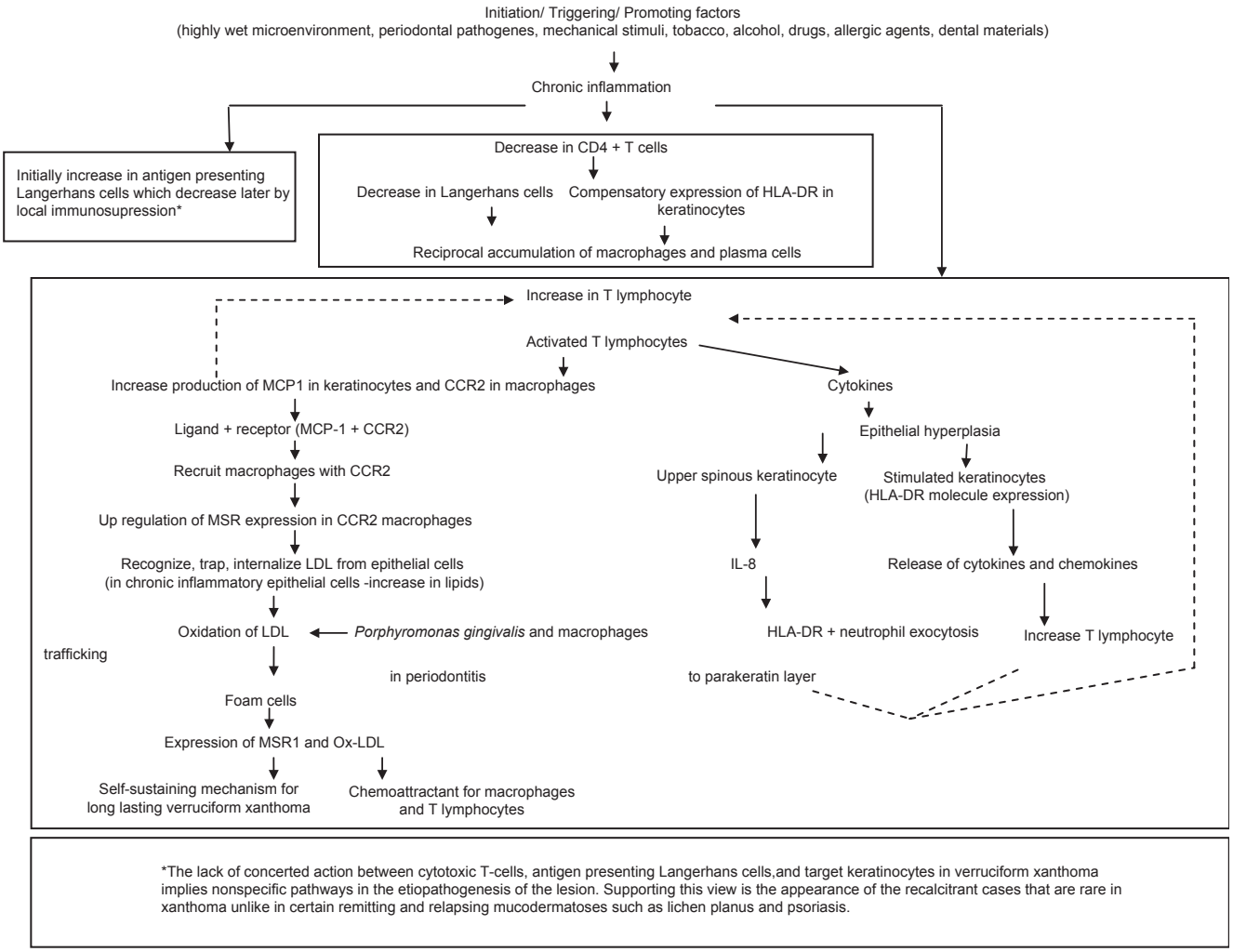

Figure 2: Verruciform xanthoma: multifactorial reactive process

Clinically, verruciform xanthoma cannot be definitively distinguished from papilloma, verruca, verrucous carcinoma and sometimes squamous cell carcinoma. However, the characteristic histopathological features helps in arriving at a conclusive diagnosis. Microscopically, a hyperplastic, parakeratinized squamous epithelium lining the papillary projections with elongated rete ridges of relatively uniform depth and the parakeratin filling the clefts or crypts between the epithelium projections will be seen. The hallmark of this lesion is the presence of numerous large macrophages with foamy cytoplasm typically confined to the connective tissue papillae, which extend high into epithelium, close to the surface known as xanthoma cells.[2] Other important features are the exocytosis of neutrophils in the parakeratin layer of epithelia and a mixed chronic inflammatory cell infiltrate in the submucosa.[20]

CONCLUSION

Verruciform xanthoma is a rare benign proliferative lesion of the oral cavity, characterized by the presence of foam cells within the connective tissue papillae. Foam cells are macrophages with lipid content, thought to be derived from the keratinocytes. They show intense positivity to CD68 antibodies suggesting the monocyte-macrophage lineage. Further these foam cells have been identified as belonging to chronic inflammatory phenotypes rather than acute inflammatory phenotypes, suggesting a chronic inflammatory mechanism.

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