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ORIGINAL ARTICLE

Cellular basis of verruciform xanthoma: immunohistochemical and ultrastructural characterization

F Ide[1,2], K Obara[1], H Yamada[1], K Mishima[1], I Saito[1], K Kusama[2]

[1]*Department of Pathology, Tsurumi University School of Dental Medicine, Yokohama, Japan;* [2]*Division of Pathology, Department of Diagnostic and Therapeutic Sciences, Meikai University School of Dentistry, Saitama, Japan*

BACKGROUND: Verruciform xanthoma (VX) holds two basic pathogenic interests: (1) Why and how do macrophage foam cells accumulate exclusively in the sub-basal papillae? and (2) What underlies the disease chronicity? Moreover, an unsolved question is which came first – epithelial hyperplasia or foam cell collection?

MATERIALS AND METHODS: We analyzed 36 oral mucosal lesions to dissect a series of linked cellular changes in VX using immunohistochemical and ultrastructural techniques.

RESULTS: Macrophage scavenger receptor-1 (MSR-1), monocyte chemoattractant protein-1 (MCP-1), CCR2, and oxidized low-density lipoprotein (ox-LDL) were all expressed by foam cells. VX epithelium showed reactivity for MCP-1, HLA-DR and IL8 in varying degrees, and showed a nearly 40% reduction in Langerhans cell density. In sub-epithelial inflammatory infiltrates, CD8+ T cells preponderated (>70%), but only a minority were positive for granzyme B (<1%). Keratinocyte/basal lamina complex exhibited disruption of basal lamina, squamatization and cytolysis of basal cells, fragmentation of desmosomes, and intraepithelial migration of macrophages. In severely inflamed papillae, necrotic foam cells were scavenged by adjacent macrophages.

CONCLUSIONS: Under synergistic regulation of T cells, MCP-1/CCR2-mediated macrophage recruitment in the sub-basal papillae and the lysosomal engulfment of epithelial lipids by MSR-1-bearing macrophages may be central in VX formation. Once developed, ox-LDL-induced foam cell necrosis and macrophage-dependent debris disposal may cyclically perpetuate VX.

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Keywords: foam cells; keratinocytes; macrophages; neutrophils; T cells; verruciform xanthoma

Correspondence: Dr Fumio Ide, Department of Pathology, Tsurumi University School of Dental Medicine, 2-1-3 Tsurumi, Tsurumi-ku, Yokohama 230-8501, Japan. Tel: +81 45 580 8361, Fax: +81 45 580 8361, E-mail: ide-f@tsurumi-u.ac.jp
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Introduction

Verruciform xanthoma (VX) is an uncommon lesion of adults with special predilection for the oral mucosa. Extraoral occurrence is much rarer and has been reported mainly involving the anogenital mucosa and the skin (Philipsen *et al*, 2003). A defining feature of VX is a massive accumulation of macrophage foam cells in the elongated connective tissue papillae between the acanthotic squamous epithelial ridges of uniform depth. Equally impressive are exocytosis of neutrophils in the parakeratin layer and infiltration of lymphocytes and plasma cells in the submucosa (Mohsin *et al*, 1998).

The etiopathogenesis of VX remains elusive to date. Previous pathologic studies investigated the fine structure (Zegarelli *et al*, 1975; Cobb *et al*, 1976; Palestine and Winkelmann, 1982; Ronan *et al*, 1984; Nakamura *et al*, 1989; Travis *et al*, 1989; Balus *et al*, 1991) and immunoprofile (Mostafa *et al*, 1993; Iamaroon and Vickers, 1996; Mohsin *et al*, 1998) of foam cells. As a result, mutual interactions among keratinocytes, macrophages, neutrophils, and lymphocytes are still uncertain. In an attempt to clarify local factors that regulate selective recruitment and persistent accumulation of foamy macrophages in the sub-basal papillae, we analyzed the cellular and molecular pathways of chronic inflammation in VX using immunohistochemical and ultrastructural techniques.

Materials and methods

Samples

Thirty-six cases of VX affecting the oral mucosa that were diagnosed in our institutions during the period 1974–2005 formed the basis of the present study. This work was conducted in accordance with a protocol approved by the Ethical Committees of Tsurumi and Meikai Universities.

Immunohistochemical analysis

Formalin-fixed and paraffin-embedded sections were stained for macrophage scavenger receptor-1 (MSR-1,

polyclonal; Chemicon, Temecula, CA, USA; 1:200), monocyte chemoattractant protein-1 (MCP-1, 5D3-F7; BD Biosciences, San Diego, CA, USA; 1:100), CCR2 (48607; R&D System, Minneapolis, MN, USA; 1:200), HLA-DR (TAL, 1B5; Dakocytomation, Carpinteria, CA, USA; 1:50), oxidized low-density lipoprotein (ox-LDL, polyclonal; Chemicon; 1:50), IL-8 (polyclonal; Abcam, Cambridge, UK; 1:100), CD1a (O10; Immunotech, Marseille, France; prediluted), CD83 (HB15e; Serotec, Oxford, UK; 1:100), CD3 (PC3/188A; Dakocytomation; 1:50), CD4 (1F6; Nichirei, Tokyo, Japan; prediluted), CD8 (C8/144B; Dakocytomation; prediluted) and granzyme B (GrB, polyclonal; Santa Cruz, Santa Cruz, CA, USA; 1:200). After microwave heat-induced epitope retrieval, the standard streptavidin-biotin complex method was applied. To characterize the lymphocyte subpopulation in the submucosa, up to 400 cells were counted and the number of immunolabeled cells was expressed as the percentage of all mononuclear cells counted. Counting of Langerhans cells was carried out in VX and non-VX epithelium at a magnification of 40×.

Ultrastructural analysis

Ten fresh lesions were fixed in 2.5% glutaraldehyde, post-fixed in 1% osmium tetroxide and embedded in Epon 812. The ultrathin sections were stained with uranyl acetate and lead citrate and examined under a JEM 100B electron microscope (JEOL Ltd, Tokyo, Japan).

Results

Clinical features

The age of 36 patients ranged from 27 to 84 years (mean 58.3 years). The female to male ratio was 1:1.6 (14/22). The gingiva/alveolar mucosa was the most frequent site (25 cases), with the following location in descending order: tongue ($n = 4$), buccal mucosa and palate ($n = 3$ each) and mouth floor ($n = 1$). One of our series was seen in a patient with hypercholesterolemia and other cases were hepatitis C virus carrier ($n = 2$) and diabetes mellitus ($n = 1$). Concomitant oral mucosal diseases were lichen planus, leukoplakia and amyloidosis ($n = 1$ each). There was no therapeutically recalcitrant case and only a single patient presented with a recurrent gingival lesion.

Histopathology

Our series showed 20 papillary, nine flat and seven verrucous types, but in any given lesion, all, some or just one of these patterns were seen. Foam cell density largely varied from lesion to lesion and papilla to papilla. In two cases, foam cells extended beyond the level of the rete ridges. In addition to lymphocytes, plasma cells were conspicuous in seven gingival VX. Two tongue lesions exhibited marked ectasia of blood and lymph vessels at the inflamed base.

Immunohistochemical findings

Foam cells were stained for MSR-1, MCP-1, CCR2, HLA-DR, and ox-LDL (Figure 1a–d), with no expression for the rest of antibodies tested. Submucosal mononuclear infiltrate consisted mostly of CD3+ T cells (>75%), with predominance of CD8+ (>70%) over CD4+ (<5%) subset (Figure 1e,f). Only a minor subpopulation expressed GrB (<1%); there was no concentration of GrB+ T cells in the interface infiltrate. VX epithelium showed expression of ox-LDL in the whole extension (Figure 1d). Localization of MCP-1 in the basal layer (Figure 1c) and IL-8 in the upper spinous layer was evident. The pattern of keratinocyte HLA-DR was variable, ranging from focal basal cell expression to entire thickness staining (Figure 1g); their intensity was correlated with the foam cell density. In normal epithelium adjacent to VX, HLA-DR was undetectable on keratinocytes. Neutrophils aggregated in the parakeratin layer expressed HLA-DR. VX epithelium showed more than 40% reduction in the

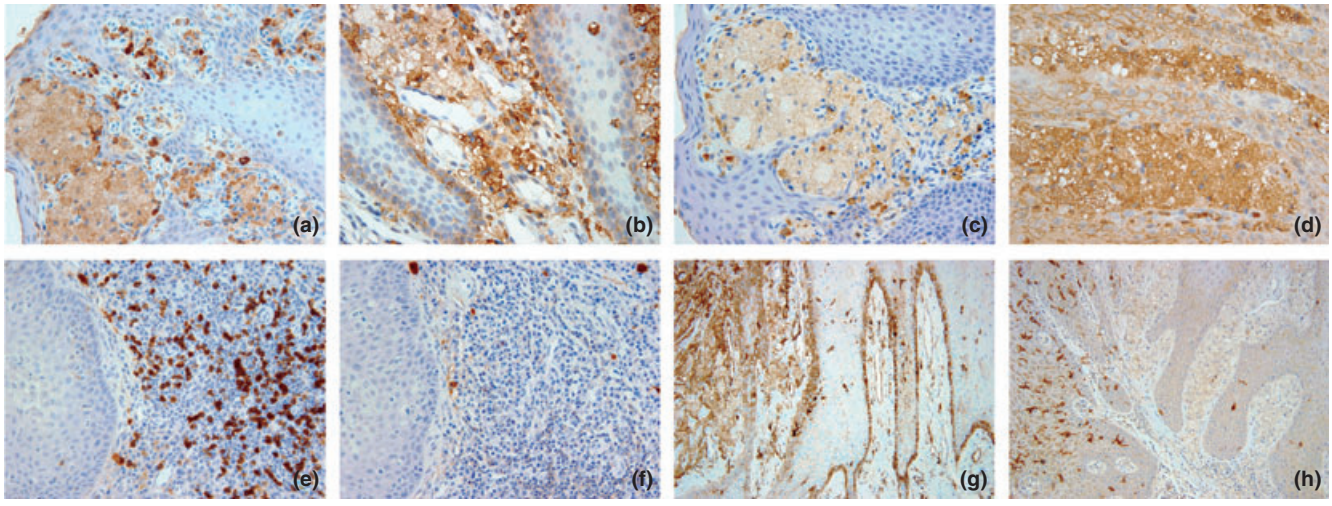

Figure 1 MSR-1 (**a**), MCP-1 (**b**), CCR2 (**c**) and ox-LDL (**d**) in foam cells. Note reactivity for MCP-1 in basal cells. CD8+ T cells (**e**) outnumber CD4+ T cells (**f**). (**g**) Varied expression of keratinocyte HLA-DR. (h) Disappearance of CD1a+ Langerhans cells (streptavidin-biotin, original magnification: **a**, **c**, **e** and **f**: ×200; **b** and **d**: ×400; **g** and **h**: ×100)

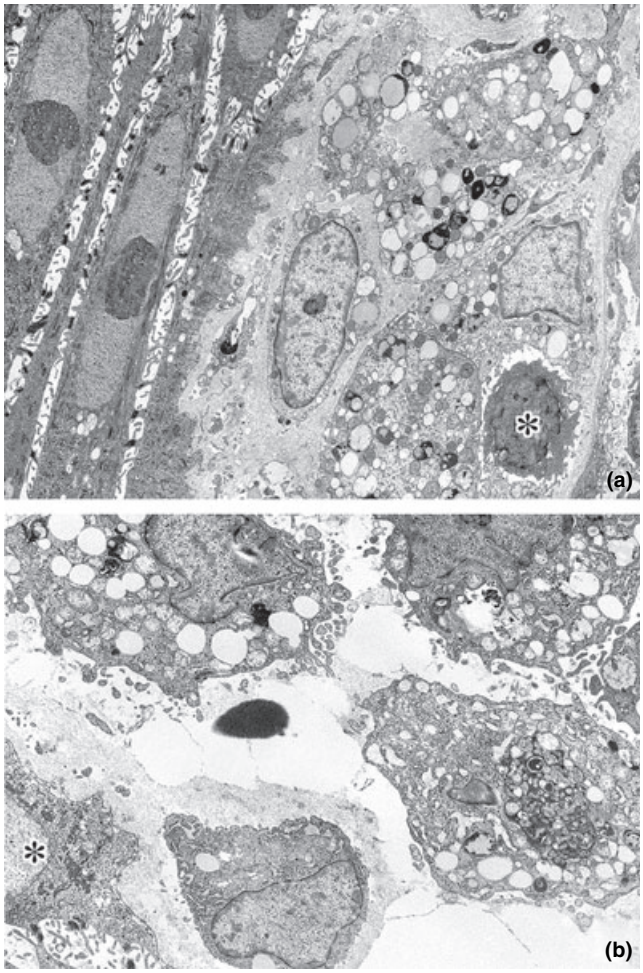

Figure 2 (**a**) Squamatization of basal cells and subepithelial accumulation of foam cells and lymphocyte (asterisk) (×2400). (**b**) Developing foam cells beneath keratinocytes (asterisk) (×3600)

number of both CD1a+ immature and CD83+ mature Langerhans cells compared with those in non-VX epithelium (Figure 1h).

Ultrastructural findings

General features

Foam cells were in close proximity to the epithelium. Basal cells showed squamatization with their long axes parallel to the basal lamina (Figure 2a). In the papillae crowded by foam cells, keratinocyte/basal lamina complex appeared intact. The other consistent feature of sub-basal papillae was numerous capillaries lined by plump endothelium and duplicated basal lamina. Lipid vacuoles were rarely observed in endothelial cells, pericytes and submucosal dendrocytes. Interestingly, edematous papillae adjacent to VX often contained developing foam cells (Figure 2b). All areas examined were devoid for mast cells and there was no viral particle in the keratinocytes. Neither Langerhans cell nor melanocyte was present in VX epithelium.

Foam cells

Foam cells were filled with cytoplasmic inclusions of varying density, which appeared to be of lysosomal and non-lysosomal form. The non-lysosomal type was electron-lucent droplets, without a membrane (Figure 3a). The others were membrane-bound and contained lipid and dense granular material. They were sometimes associated with myelin figures, and some resembled residual bodies (Figure 3a,b). Collectively, the majority of foam cells were macrophage in origin, whereas a minority were transformed fibroblasts (Figure 3c). Fully distended macrophage foam cells frequently showed ultrastructural signs of necrosis including rupture of nuclear and cell membranes (Figure 4a). Extracellularly released cytoplasmic contents were successively scavenged by nearby macrophages with numerous ruffled cell processes (Figure 4b). Phagocytosed dying cells were present in foam cells (Figure 4c).

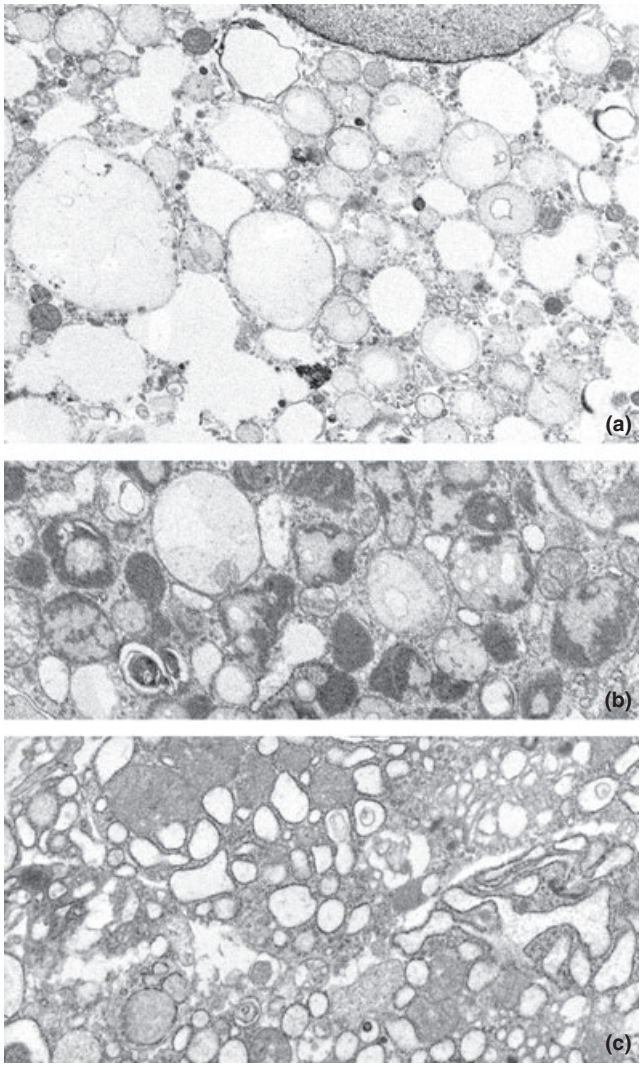

Figure 3 (**a**, **b**) Membrane-bounded vacuoles are derived from multivesicular lipid bodies (**a**: ×6000; **b**: ×9000). (**c**) Empty vacuoles are cystically dilated rough endoplasmic reticulum (**c**: ×7200)

Keratinocyte/basal lamina complex

Morphologic alterations at the epithelial–connective tissue interface were quite different from case to case and area to area. In general, partial loss of basal lamina

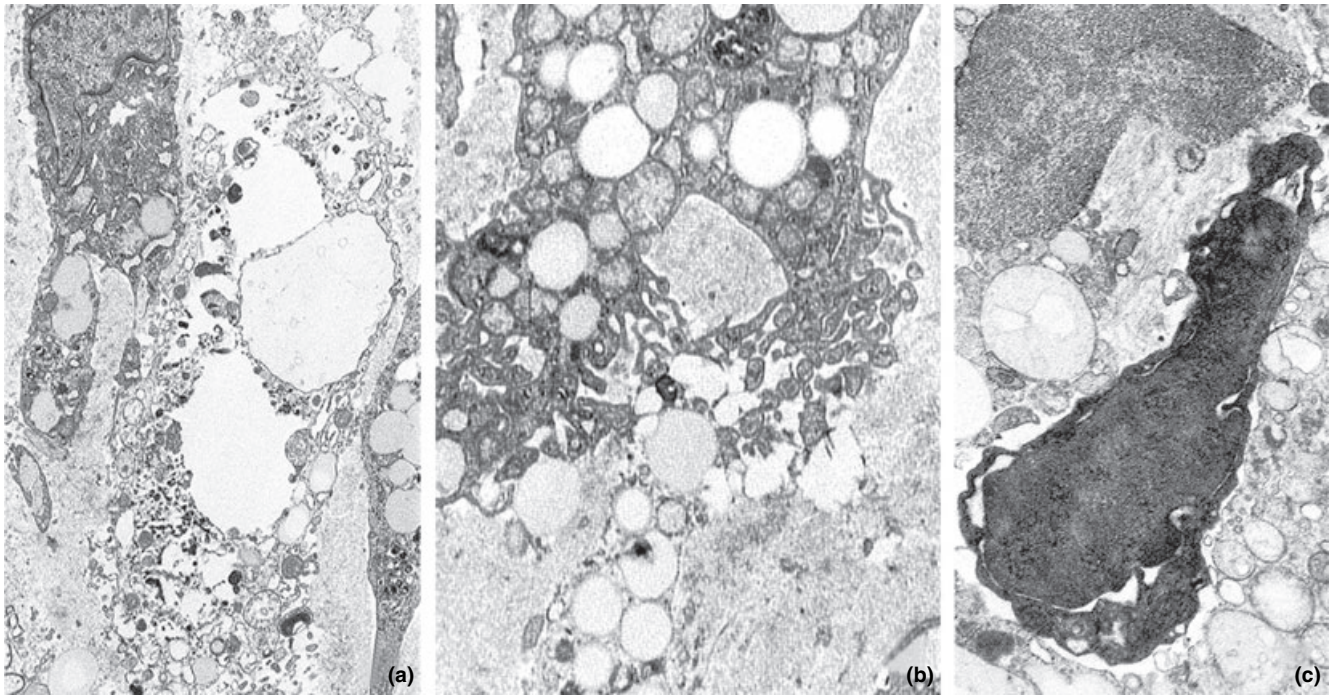

Figure 4 (**a**, **b**) Necrotic foam cells phagocytosed by macrophages (×6000). (**c**) Dying cell in foamy macrophage (×10800)

and hemidesmosomes was evident in the spongiform VX epithelium and fragments of basal lamina lay freely in the sub-basal papillae (Figure 5a–c). In the foam cell-free papillae, irregular branching of keratinocyte/basal lamina complex and cell-to-cell contact between degenerating basal keratinocytes and macrophages could readily been seen (Figure 5a,d). Accompanied by desmosome fragmentation, keratinocytes formed numerous long microvilli protruding into the widened intercellular spaces (Figure 5a,b,d). In many areas, macrophages migrated into the lower layer of the epithelium and possessed a foamy appearance with numerous residual bodies (Figure 6a,b). Frequently, intraepithelial foam cells degenerated and released lipid droplets into the sub-basal papillae with disruption of basal lamina (Figure 6c).

Discussion

Verruciform xanthoma is a superficial normolipidemic xanthoma of squamous mucosa and skin (Herrera-Goepfert *et al*, 2003; Philipsen *et al*, 2003), pointing to the spatial interaction between keratinocytes and macrophages. Though not fully explored, we construct testable hypotheses of the immunopathogenesis of VX, combining the previous information and present findings.

Psoriasiform hyperplasia of keratinocytes may be initiated and maintained by T cell-mediated inflammation

Because of the magnitude of infiltration (Mostafa *et al*, 1993; Iamaroon and Vickers, 1996), it is impossible to escape the conclusion that T cells found a milieu of disease characteristics of VX. The expression of HLA-DR molecule in the psoriasiform epithelium appears to be immunophenotypic activation by T cell-secreted cytokines (Iamaroon and Vickers, 1996; Travers *et al*, 1999; Myint *et al*, 2000). Stimulated keratinocytes may be responsible for releasing cytokines and chemokines which in turn enhance trafficking of additional T cells. In parallel, IL-8 production by the upper spinous keratinocytes suffices to induce neutrophil exocytosis in the parakeratin layer (Garlet *et al*, 2003). HLA-DR + neutrophils further augment the activation state of T cells (Travers *et al*, 1999). This complicated cascade may form a vicious loop for the persistence of epithelial hyperplasia and T cell infiltration in chronic VX.

MCP-1/CCR2 axis directs macrophage influx into the sub-basal papillae

MCP-1, a potent monocyte/macrophage attractor, is localized in the basal cells of VX. Activated T cells are the major subset capable of modulating the MCP-1 production by keratinocytes (Garlet *et al*, 2003; Vestergaard *et al*, 2004). In addition to MCP-1, its shared receptor CCR2, which up-regulates macrophage and T cell trafficking (Vestergaard *et al*, 2004), is constitutively expressed in foam cells. Thus, the ligand–receptor pair of MCP-1 and CCR2 may serve as a master inducer of macrophages in the sub-basal papillae. The intriguing proclivity of oral VX for the gingiva could be explained in part by the fact that the most prevalent chronic inflammatory diseases in adults, gingivitis and periodontitis, are examples of both T cell activation, expansion and polarization, and keratinocyte expression of MCP-1, HLA-DR and IL-8 (Myint *et al*, 2000; Garlet

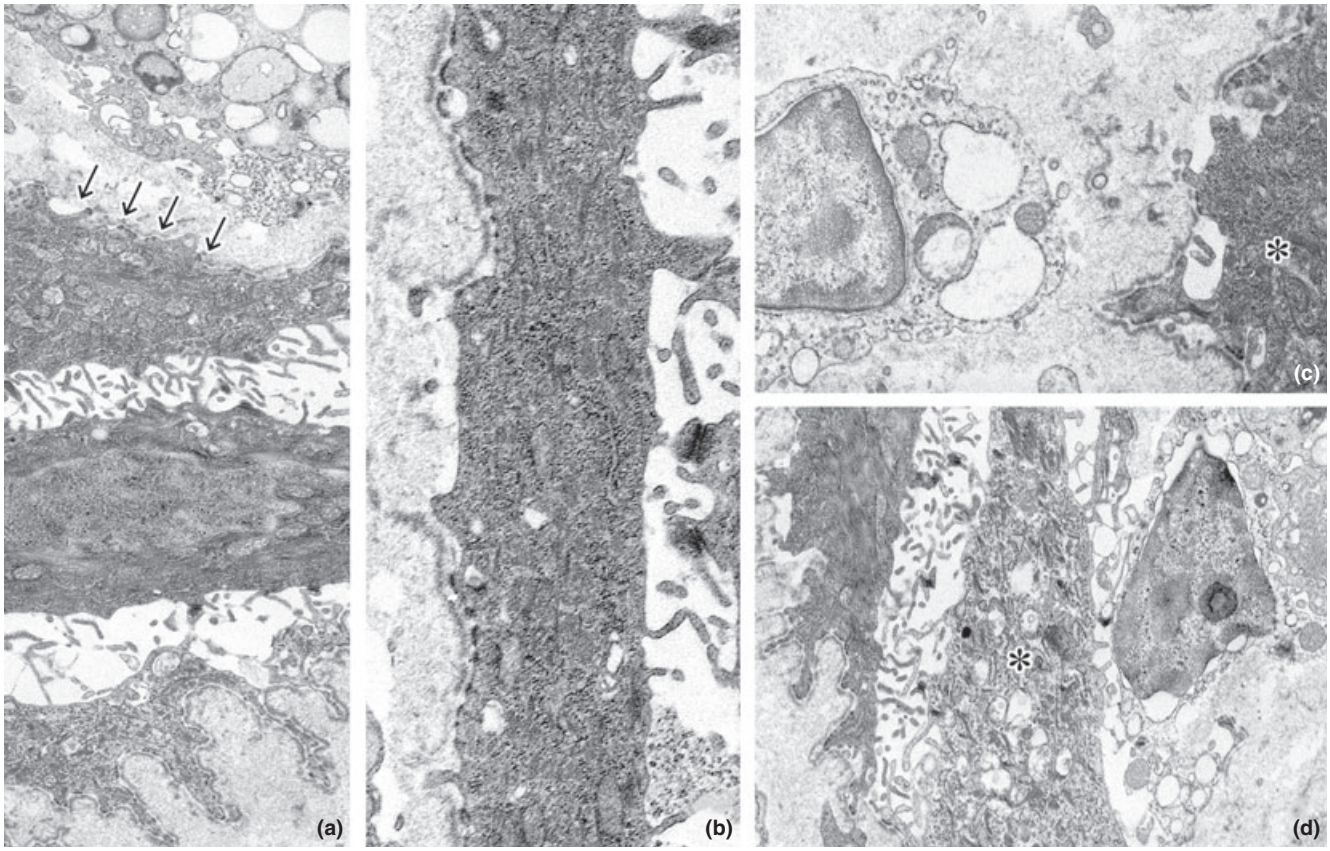

Figure 5 (**a**) Loss of basal lamina (arrows) in foamy papilla (×6000). (**b**) Disruption of hemidesmosome and basal lamina (×12000). (**c**) Basal lamina fragmentation of keratinocyte (asterisk) (×9000). (**d**) Keratinolysis (asterisk) by macrophage (×5400)

et al, 2003). Interestingly, periodontitis-associated bacteria, *Porphyromonas gingivalis*, can up-regulate the secretion of MCP-1 and IL-8 (Kuramitsu *et al*, 2002).

Different mechanisms may be involved in the degeneration/destruction of keratinocyte/basal lamina complex

There are many reports on VX occurring within a variety of underlying mucocutaneous diseases which affect turnover and maturation of keratinocytes (for review, see Philipsen *et al*, 2003; Wu *et al*, 2006). These inherent or acquired conditions are known to drive the keratinocyte degeneration. We assume that basal squamatization in VX is not a simple mechanical flattering by foam cell pool (Mostafa *et al*, 1993), but an important morphologic sign of chronic epithelial damage, because of a common feature of interface mucodermatoses. As clearly shown, macrophages directly cleaved the keratinocytes. As the morphologic changes of keratinocyte/basal lamina complex are dynamic and very intricate, the ultrastructural chance finding of intact basal lamina may be the temporal sequence of the ongoing process (Travis *et al*, 1989). Given the fact that psoriasis which share similar intraepithelial neutrophil aggregates rarely progress to VX (Smith *et al*, 1995; Yamamoto *et al*, 1995; Mohsin *et al*, 1998), the pathogenic significance of neutrophils may be marginal. Unlike lichen planus, a great scarcity of GrB+ cells in VX underscores the possibility that T cell-mediated cytotoxicity plays a minor role in the basal lamina disruption and keratinolysis.

Lipids may be released from the degenerating keratinocyte/basal lamina complex

The key to clarify the disease pathophysiology of VX lies in the clarification of lipid source. The serum lipoprotein origin is supported by VX developed on a background of chronic local circulatory disturbance (Huguet *et al*, 1995; Kishimoto *et al*, 1998; Wu and Wagner, 2003). In our opinion, certain histologic differences can be appreciated from the figures in these cases and this theory does not satisfactorily explain why foam cells selectively target to the sub-basal papillae. Squamous epithelia are active sites of lipid biosynthesis (Uchiyama *et al*, 2000) and epidermal lipids are increased in chronic inflammatory dermatoses including VX (Shindo *et al*, 1985; Uchiyama *et al*, 2000). Both membrane-bounded vacuoles in the keratinocytes (Zegarelli *et al*, 1975; Ronan *et al*, 1984; Nakamura *et al*, 1989; Balus *et al*, 1991) and foamy macrophages in the epithelium (Zegarelli *et al*, 1975; Cobb *et al*, 1976; Ronan *et al*, 1984), as we demonstrated, may offer ultrastructural evidence that lipids are epithelial in origin. Of interest is the recent report that genetic alterations of 3β-hydroxysteroid dehydrogenase are associated with a small subset of cutaneous VX (Mehra *et al*, 2005).

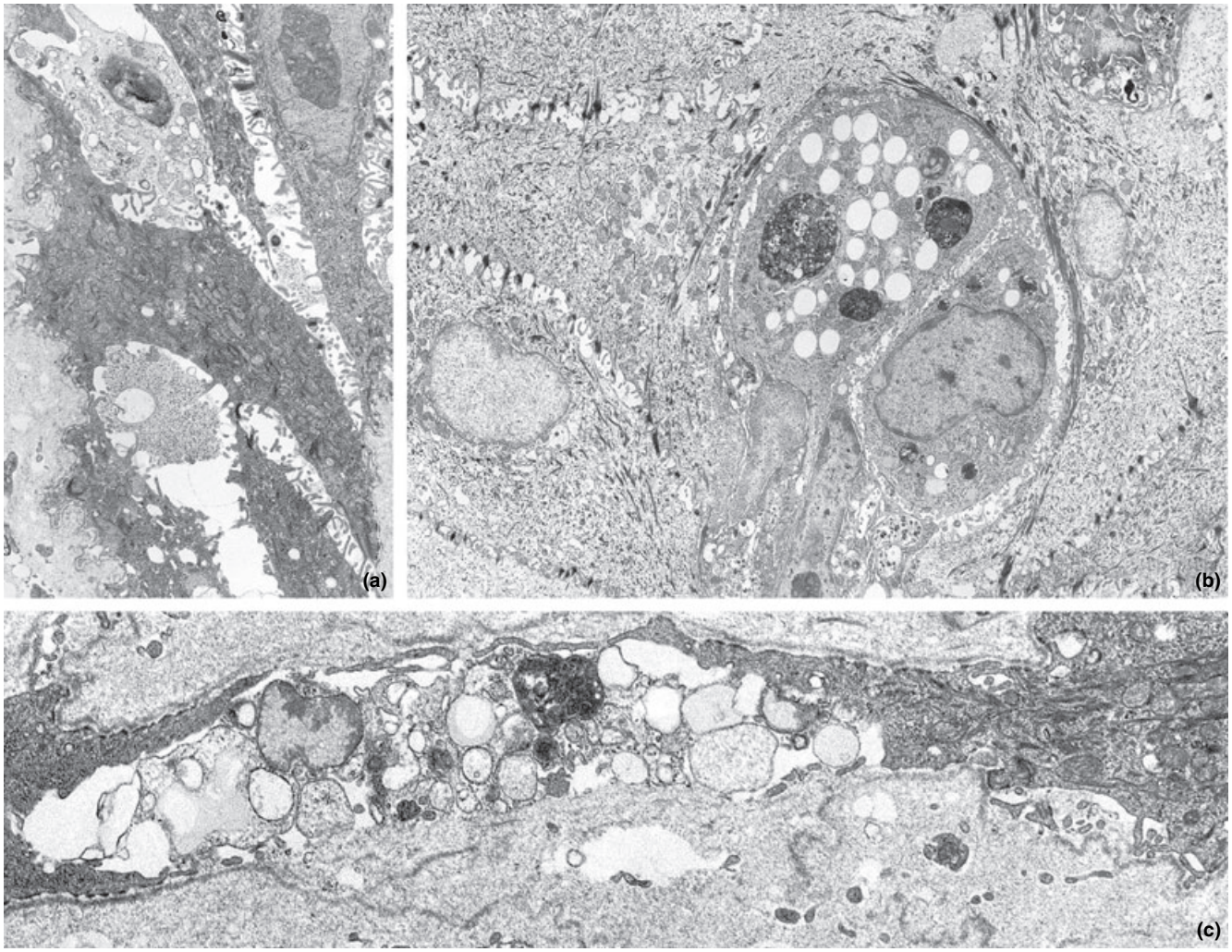

Figure 6 (**a**) Intraepithelial migration of macrophages (×3600). (**b**) Foamy macrophages within epithelium (×3300). (**c**) Rupture of intraepithelial foam cell with disruption of basal lamina (×6900)

MCP-1/ox-LDL-inducible expression of MSR-1 governs transformation of CCR2-bearing macrophages into foam cells

MSR-1 and ox-LDL are expressed in foam cells. Ox-LDL is known to be a potent chemoattractant for macrophages and T cells (Tabata *et al*, 2003; Robbesyn *et al*, 2004). MCP-1 and ox-LDL up-regulate MSR expression in CCR2+ macrophages and activated MSR serves to recognize, trap and internalize LDL (Tabata *et al*, 2003). It is likely that macrophages in VX take up LDL without negative feedback via MSR-1 and are finally converted into foam cells (Furue *et al*, 1995). A cautionary note is the observation that the interaction of *P. gingivalis* with macrophages could lead to the oxidative modification of LDL, resulting in the foam cell formation (Kuramitsu *et al*, 2002). As macrophages themselves oxidize LDL sufficiently to produce self-inflicted toxicity (Robbesyn *et al*, 2004), the inflammatory burst elicited by foam cell necrosis, as depicted in the ultrastructural result, exacerbates a local macrophage trafficking. This potential self-sustaining mechanism contributes in part to the maintenance of long-lasting VX.

Both antigen-specific and nonspecific mechanisms may combine to cause VX

Based on the present data, VX may be conceptualized as an atypical T cell-mediated immune response to altered keratinocytes. It is interesting to note that in contrast to lichen planus, intraepithelial Langerhans cell density is very low in VX (Mostafa *et al*, 1993; Furue *et al*, 1995; Polonowita *et al*, 1999; Kanitakis *et al*, 2004). At the ultrastructural level, Balus *et al* (1991) failed to find, as we did, any lesional cells identical to Langerhans lineage. One plausible explanation for this puzzling phenomenon is that when VX develops, Langerhans cells initially increase but gradually decrease via local immunosuppression (Kanitakis *et al*, 2004). Another possibility is that significant reduction in CD4+ T cells may be responsible for loss of Langerhans cell network, compensatory expression of HLA-DR in keratinocytes and reciprocal accumulation of macrophages and

plasma cells (Myint *et al*, 2000). In any event, considering the lack of concerted action between cytotoxic T cells, professional antigen-presenting Langerhans cells and target keratinocytes in VX, nonspecific pathways seem to be active. Supporting evidence is that unlike autoimmune remitting and relapsing mucodermatoses such as lichen planus and psoriasis, a widespread recalcitrant case appears seldom in VX (Sopena *et al*, 2004).

VX may be a multifactorial reactive process unrelated to human papillomavirus (HPV)

It is a consensus of opinion that there is little published evidence in support of an etiological link between HPV infection and development of VX (Philipsen *et al*, 2003; Mehra *et al*, 2005). We confirmed, albeit in only 10 cases, the absence of virus particles. A marked heterogeneity of clinical settings offers an alternative explanation that VX may be a unique reaction pattern (for a review, see Philipsen *et al*, 2003; Wu *et al*, 2006). Presumably, an initiation event varies from site to site or patient to patient. We speculate that under the highly wet microenvironment, periodontopathic pathogens, mechanical stimuli, tobacco, alcohol, drugs, sensitizing or allergic agents of foodstuffs and dental materials are likely to play a pathogenic role in triggering and/or promoting oral VX formation.

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