REVIEW ARTICLE

Etiopathogenesis of Oral Lichen Planus: Highlighting the Role of T Cells, Mast Cells, RANTES, and Matrix Metalloproteinases

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Abstract

Oral lichen planus (OLP) is an autoimmune chronic inflammatory disease that affects the mucous membrane of the oral cavity. It is mediated by T cells, causing the basal cells of the oral epithelium to undergo apoptosis through the action of cytotoxic CD8+ T cells. A number of inflammatory mechanisms have been proposed to explain the subepithelial accumulation of CD8+ T cells as well as the death of keratinocytes that follows. This paper reviews the numerous theories on the etiopathogenesis of OLP and highlights the role of T cells, mast cells, RANTES, and matrix metalloproteinases (MMPs).

Keywords: oral lichen planus, etiology, pathogenesis, histology.

Introduction

Oral lichen planus (OLP) is a chronic inflammatory disease that affects the mucous membrane of the oral cavity. It belongs to the mucosal counterpart of cutaneous lichen planus [LP] (1, 2). Although the prevalence of cutaneous LP ranges from 0.22 to 1% and equally affects people of both sexes (3), OLP is more frequent and is reported in 2% to 5% of the general population, with a female-to-male ratio of 2:1 (4-7). Additionally, while cutaneous LP is not usually considered to have a racial predilection, some studies have suggested a higher incidence of the disease in African American, Indian and Arabian descents (8,9), and a familial component of up to 10% of first-degree relatives has been proposed (10). In terms of OLP, non-Asian populations present a greater incidence (11). LP typically appears in adults aged 30 to 60 years and occasionally involves other age groups (5).

The etiopathogenesis of OLP has been extensively investigated, and several mechanisms have been proposed to explain it. In this review, we discuss the most recent theories on the etiopathogenesis of OLP and highlight the roles of T cells, mast cells, RANTES, and matrix metalloproteinases (MMPs).

Clinical Features of LP and OLP

LP can possibly affect the skin, the lips, the oral mucosa, the esophagus, the pharynx, and the genital mucosa (the glans penis, the vulvar and vaginal mucosa, the labia majora, and the labia minora) (12). Additionally, LP may involve the scalp hair follicles (lichen planopilaris) in the form of inflammation and keratotic papules, eventually leading to scarring alopecia (13). Furthermore, the disease may affect some or all nails through longitudinal ridging, splitting, thinning, and, in the extreme cases, pterygium formation (14).

While the cutaneous disease has numerous clinical variants, it mostly presents as small, sharply demarcated, flattened, and polygonally shaped erythematous-livid papules (5). Another notable characteristic of LP is the epidermal hypergranulosis, which appears as whitish reticulate structures or Wickham's striae on the surface of the lesions (15). Typically, a classic LP manifests as a localized form affecting just the extremities, primarily the lumbar area, wrists, ankles, and dorsal surfaces of the hands and feet (15). Less frequently, it manifests as a widespread condition that affects the entire body, including the anogenital areas and the oral mucosa (5). Severe pruritus that is as intense as the affected area without apparent scratches or subsequent infections generally follows cutaneous LP (6).

OLP that occurs either associated with the classic cutaneous disease (70% of cases) or without (20 to 30% of cases) may appear in six different forms, namely reticular, papular, plaque-like, atrophic/erosive, ulcerative, and bullous; the reticular one predominates (Figure 1), followed by the erosive form, characterized by pain, a chronic, recalcitrant course, and possible malignant transformation into squamous cell carcinoma (7, 16).

Intraorally, the buccal mucosa, tongue, and gingiva are commonly involved, although other sites may be rarely affected (17).

Etiology and Pathogenesis of OLP

While the precise etiology of OLP is unknown, factors such as stress, immunity, genetics, hypersensitivity reactions, and medications including beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), thiazide diuretics, quinidine, antimalarials, and tumor necrosis factor alpha (TNFα) inhibitors may all be involved (1, 8). Additionally, many metals that are present in dental restorations, such as gold, copper, and mercury, are thought to be etiologic factors as well (18, 19).

Furthermore, over 90 controlled studies conducted worldwide, especially in the USA, Japan, and southern Europe, have found a connection between the hepatitis C virus (HCV) and the development of OLP (2, 9, 18). In fact, in OLP, HCV replication has been shown in the subepithelial band by HCV-specific CD4 and CD8 lymphocytes, as well as in the epithelial cells from the mucosa of LP lesions using reverse transcription/polymerase chain reaction or in-situ hybridi-

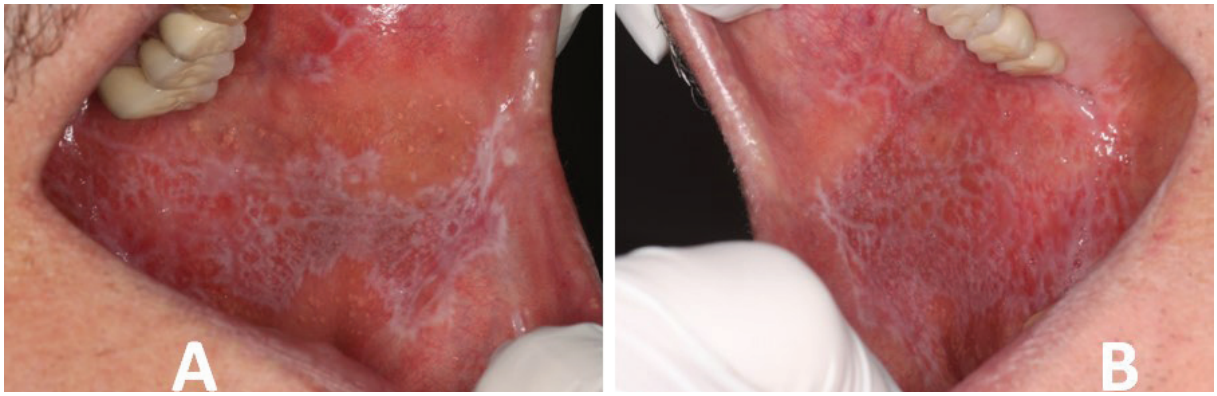

Figure 1. Intraoral photographs showing bilateral buccal reticular lesions

zation (2, 20).

Regarding the pathogenesis of OLP, numerous studies have suggested that OLP is a T cell-mediated autoimmune condition, wherein auto-cytotoxic CD8+ T cells trigger apoptosis of the basal cells of the oral epithelium (10). The early steps of the disease mechanism involve keratinocyte antigen expression or the unmasking of an antigen that may be a self-peptide or a heat shock protein (2, 21). After that, T cells (mostly CD8+ and some CD4+ cells) migrate into the epithelium as a result of either a random encounter of antigen during routine surveillance or a chemokine-mediated migration toward basal keratinocytes (2, 22). These migrated CD8+ cells are activated directly by antigen binding to major histocompatibility complex (MHC-1) on keratinocyte or throughout activated CD4+ lymphocytes (2). Additionally, the number of Langerhans cells in OLP lesions is increased along with upregulation of MHC-II expression; subsequent antigen presentation to CD4+ cells and Interleukin-12 (IL-12) activates CD4 + T helper cells which activate CD8+ T cells through receptor interaction, interferon γ (IFN- γ) and Interleukin-2 (IL-2). The activated CD8+ T cells in turn kill the basal keratinocytes through TNF-α, Fas–FasL mediated or granzyme B (GrB) activated apoptosis (2, 21, 22).

The normal integrity of the basement membrane is maintained by a living basal keratinocyte because of its secretion of both collagen 4 and laminin 5 into the epithelial basement membrane zone. Sequentially, keratinocytes require a basement membrane-derived cell survival signal to avoid the commencement of its apoptosis. Apoptotic keratinocytes are no longer able to achieve this function, which results in disruption of the basement membrane. Similarly, a disrupted basement membrane cannot send a cell survival signal. This sets in a vicious cycle which relates to the chronic nature of the disease (2, 22, 23).

On the other hand, it has been found that OLP exhibits weak expression of transforming growth factor (TGF)-β1whose deficiency may predispose to autoimmune lymphocytic inflammation. The equilibrium between TGF-β1 and IFN-γ establishes the level of immunological activity in OLP lesions. A local increase in the production of IFN-γ by CD4+ T cells attenuate the immunosuppressive effect of TGF-β1 and stimulates keratinocyte MHC class II expression and CD8+ cytotoxic T-cell activity (2, 22, 23).

Furthermore, the chemokine RANTES (Regulated on Activation, Normal T-cell Expressed and Secreted), part of the CC chemokine family which plays a significant role in the recruitment of lymphocytes and mast cells has been identified binding to cell-surface receptors CCR1, CCR3, CCR4, CCR5, CCR9, and CCR10 in OLP. The recruited mast cells undergo degranulation under the influence of RANTES and release chymase, tryptase, and TNF-α, consequently upregulating RANTES secretion. This again sets in a vicious cycle, which relates to the chronic nature of the disease (22).

Moreover, the matrix metalloproteinases (MMPs) are principally involved in tissue matrix protein degradation. MMP-9, which cleaves collagen-4, along with its activators, is upregulated in OLP lesional T cells, resulting in increased basement membrane disruption (21).

Histology of OLP

Histological features of OLP may include a thickened stratified epithelium with irregular acanthosis, hyperparakeratosis, and formation of parakeratosis foci. Additionally, a dense band-like inflammatory infiltrate consisting of mononuclear cells and a perturbation of the basement membrane integrity are observed [24].

Conclusion

OLP is an immune disease with unknown etiology. Its pathogenesis may especially involve cytotoxic CD8+ T cells that release different

cytokines, leading to the disruption of the lining epithelial basement membrane. The indirect action of mast cells, RANTES, and MMPs was identified in the pathogenesis of OLP.

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