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Review

Oral lichen planus: Malignant potential and diagnosis

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ABSTRACT

Oral lichen planus (OLP) is one of the most common diseases of the oral mucosa. Clinically, it has specific and clearly identifiable features; bilateral symmetric presentation showing a lace-like network of fine white lines (known as Wickham's striae) is an essential element of OLP even if the lesion exhibits a mainly atrophic and erosive pattern. There are various lesions that resemble OLP clinically and histologically. These lesions are widely referred to as lichenoid reactions or lichenoid lesions (OLLs). OLLs include contact hypersensitivity to dental materials, drug-induced lichenoid lesions, lichenoid reactions in chronic graft-versus-host disease, and other lesions that resemble OLP. The risk of malignant transformation of OLP is the subject of ongoing debate in the literature. Some authors have suggested that only OLLs, but not OLP, are of a premalignant nature and thus, should be categorized as "other dysplastic conditions." Contrary to this suggestion, many cases of oral squamous cell carcinoma (OSCC) developing in patients with OLP presenting with no epithelial dysplasia have been reported. In addition, it has been reported that multiple events including multifocal dysplasia and/or OSCC subsequently occurred in some patients with OLP, suggesting possible field cancerization in OLP. In this paper, differential diagnosis between OLP and OLLs and their malignant potential are reviewed.

Contents

1. Introduction

Various white-and-red lesions occur in the oral mucosa, including leukoplakia, erythroplakia, candidiasis, geographic tongue, lichen planus, lichenoid lesions, and others. Oral leukoplakia and oral erythroplakia are well known to be precancerous lesions [1,2], while the malignant potential of oral lichen planus (OLP) and/or oral lichenoid lesions (OLLs) has been the subject of much discussion in the past few decades [3–45]. Since the clinical and histological features of these white-and-red lesions are similar, differential diagnosis of them is important.

Lichen planus is a chronic inflammatory mucocutaneous disease associated with immune-mediated pathogenesis [3–6]. It most commonly affects the oral mucosa, but can involve other sites such as the skin, genital mucosa, scalp, and nails [4–8]. Most cases of OLP do not involve lesions at other sites. The prevalence rates of OLP vary from 0.5% to 2.6% of the world population [3–6].

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The mean age of OLP onset is the fifth decade of life, and there is a gender predilection with a female/male ratio of 2 to 3:1 [4–45]. The clinical presentation is almost always in a bilateral, symmetric pattern. The lesions are almost always seen at the buccal mucosa, and other sites including the gingiva, tongue, and lip mucosa may also be affected. Clinical features of OLP range from asymptomatic reticular white lesions in atrophic mucosa, to erosive-ulcerative areas accompanied by pain and discomfort, while the most characteristic feature is the presence of a lace-like network of fine white lines.

One of the most important issues concerning OLP is the question of its potential for malignant transformation into oral squamous cell carcinoma (OSCC). This controversial issue includes diagnostic criteria of OLP that require further discussion. In this paper, differential diagnosis and malignant transformation of OLP are reviewed.

2. Etiopathogenesis

2.1. Cell-mediated immunity

Although the exact etiology of OLP remains uncertain, cumulative evidence suggests that cell-mediated immunity plays a major role in the pathogenesis of OLP [3,7,46–56]. An immunological process is believed to be triggered by an antigen that alters the basal keratinocytes of the oral mucosa. Keratinocyte antigen expression is induced by systemic drugs, contact allergen in dental restorative materials, mechanical trauma, bacterial or viral infection, or unidentified agents. Cytotoxic $CD8^+$ T lymphocytes induce keratinocyte apoptosis through immunoreactions triggered by one or more antigens associated with major histocompatibility complex (MHC) class I on basal keratinocytes [46–49]. The activated $CD8^+$ T cells secrete tumor necrosis factor (TNF)-alpha, which binds to the TNF-alpha receptor on keratinocytes, and then keratinocyte apoptosis occurs via the caspase cascade pathways [49–52]. Helper $CD4^+$ T lymphocytes, which are activated by MHC class II associated with Langerhans cells and keratinocytes, promote the cytotoxicity of $CD8^+$ T lymphocytes through various cytokines including interleukin (IL)-2, IL-12, and interferon gamma [3,47,53].

Mast cells and antigen-presenting Langerhans cells are also involved in the local response. Activated chymase released by degranulation of mast cells acts as a matrix metalloproteinase which degrades the extracellular matrix of basement membrane and contributes to the migration of lymphocytes to the connective tissues underneath the epithelial layer in OLP [54–56].

2.2. Association with hepatitis C virus

Some reports have suggested a possible association between OLP and viral infections, such as herpes simplex virus, Epstein–Barr virus, human papilloma virus [59,60], and hepatitis C virus (HCV) [61–77]. The most extensively studied virus is HCV, but its association with OLP remains controversial. High prevalence rates of HCV infection in patients with OLP have been demonstrated in certain populations, mainly in the Mediterranean [61–63] and Asia [64–66], while this association between OLP and HCV is not found in other areas, such as Northern Europe [67–70], suggesting geographic heterogeneity [71]. One explanation for the geographic differences may be genetic predisposition. For example, a higher frequency of the class II MHC allele, DR6, has been reported in Italian OLP patients with HCV compared with those without HCV [72,73]. Contrary to expectations, a low incidence of OLP in an area of southern Italy where HCV infection is hyperendemic has been also reported [74].

A pathogenic role of HCV infection in OLP is still uncertain. Detection of HCV RNA in the mucosal lesions of patients with OLP [75,76], and the presence of HCV-specific $CD4^+$ and $CD8^+$ T lymphocytes in OLP lesions [77] suggest that epithelial cells expressing HCV antigens may be targets for the immunopathogenesis of OLP. Another relevant issue is that OLP can be induced and/or aggravated by antiviral treatment with either interferon-alpha or interferon-alpha/ribavirin for HCV infection [78]. Additional reports indicate an association between OLP and liver diseases in the absence of HCV infection [79].

Further investigations taking into account factors including HCV genotype, race, area, age, gender, treatment (before or after), and accessory co-infections such as candidiasis, are required to clarify the role of HCV in OLP pathogenesis.

3. Clinical features

Clinically, OLP has specific and clearly identifiable features [3–10]. OLPs are a mixture of white and red lesions that usually exhibit multiple foci and almost always a bilateral symmetric pattern. The most common site affected is the buccal mucosa, and some cases involve other oral mucosal sites such as the tongue, gingivae, and lower lip (in decreasing order of frequency). Lesions on palate, oral floor, and upper lip are not common.

White lesions have a reticular, papule, plaque-like appearance, and red lesions can appear atrophic (erythematous), erosive (ulcerated), or bullous-like. OLP can be divided into the aforementioned six types (reticular, papule, plaque, atrophic, erosive, and bullous types), or two types, white and red, while it is most commonly classified into three types, reticular, atrophic, and erosive (Fig. 1A–C). Lesions are not homogenous and some cases may present as a mixture of these clinical subtypes. White lesions generally form on a diffuse erythematous background. Reticular form, which is the most common type and a characteristic feature of OLP, shows a lace-like network of fine white lines (known as Wickham's striae). Plaque forms appear as homogenous white patches resembling leukoplakia. This form is often observed in the dorsum of the tongue and the buccal mucosa. The presence of striation in plaque forms may help to distinguish them from leukoplakia. The papular form consists of pinpoint white lesions, and is rarely seen.

The erosive form is the next most common type, and is also a significant one for OLP. This form presents as atrophic and erythematous areas with partial ulceration, which are often surrounded by fine white lines. When erosion is severe, the epithelium ruptures as in the case of benign mucous membrane pemphigoid. This type, known as bullous form, is very rare. Atrophic form appears as a diffuse red lesion with mucosal atrophy. Symptoms of burning or painful etching sensation are commonly associated with red lesions including atrophic (erythematous) and erosive (ulcerated) types.

If erosive forms of OLP are confined to the gingival mucosa, the condition is usually referred to as desquamative gingivitis [45,46,57,58]. Such cases should be biopsied to distinguish them from benign mucous membrane pemphigoid, pemphigus vulgaris, and other malignancies.

The World Health Organization (WHO) devised a set of diagnostic criteria for OLP in 1978 (Table 1) [2] that was revised in 2003 (Table 2) [10]. The modified WHO diagnostic criteria involve differentiation between OLP and OLLs. In these modified WHO criteria, the essential clinical feature of OLP is defined to be the presence of bilateral lesions that exhibit a lace-like network of white lines (reticular pattern), but not of plaque, atrophic, erosive, and bullous lesions. When the bilateral reticular lesion is absent, then, it is designated as "clinically compatible with OLP".