REVIEW ARTICLE

Oral lichen planus to oral lichenoid lesions: Evolution or revolution

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ABSTRACT

The diagnosis between different diseases may be impaired by clinical and histopathologic similarities, as observed in the oral lichen planus (OLP) and oral lichenoid lesion (OLL). Inspite of similar clinicopathological features; etiology, diagnosis and prognosis differ which mandates separation of OLL from OLP. Hence, it is essential for the oral physician and oral pathologist to be familiarized with the individual variations among clinicopathological features of OLP and OLL as well as to obtain a thorough history and perform a complete mucocutaneous examination in addition to specific diagnostic testing. The difficulties faced to establish the diagnosis between these two pathologies are widely investigated in the literature with a lack of definite conclusion. This review is an attempt to throw some light on these clinicopathologic entities with the aim to resolve the diagnostic dilemma.

Key words: Lichen planus, oral lichen planus, oral lichenoid lesions

INTRODUCTION

Lichen planus (LP) is a common chronic mucocutaneous inflammatory disorder of unknown etiology which frequently affects the oral mucosa.[1-7] It was first described in 1869 by Erasmus Wilson as "lichenplanus," because the clinical appearance of these lesions is similar to lichens (i.e. symbiotic algae and fungi growing on rocks).[2,8-10] Pinkus published the first microscopic description of lichenoid reactions in 1973.[8] The term oral lichenoid lesion (OLL) was proposed by Finne *et al* in 1982.[11] The term oral LP (OLP) is now considered to represent those lesions where no trigger can be identified and are hence "idiopathic, whereas all other oral lesions that are associated with drug intake, systemic disease (such as chronic liver disease), food or flavor allergies, hypertension and diabetes mellitus are considered as OLL.[12,13] Given the overlapping clinical and histopathological features, similar therapies may be used in all of these conditions. However, unlike OLP, OLL resolves after discontinuation of the causative agent.[2,4] Distinguishing these OLL from one another is also mandatory as some of the OLL, such as graft versus host disease (GVHD) and amalgam associated lichenoid reaction, have a high propensity for malignancy.[14] However, the differentiation is not always straight forward.[1,3,5] The difficulties faced to establish the diagnosis between these pathologies are widely investigated in the literature with a lack of definite conclusion. This review is an attempt to throw some light on these clinicopathologic entities with the aim to resolve the diagnostic dilemma.

ORAL LICHEN PLANUS

OLP affects 0.5–2% of the population.[2-5,9,13,15] However, the figure depends on the population studied.[2-5,7] The prevalence of OLP in the general population ranges between 0.5% in a selected Japanese population, 1.9% in the Swedish population and 2.6% in the Indian population.[16] Epidemiological studies are hampered by lack of clear diagnostic criteria; varied clinical presentation; and the fact that the most common form of OLP, reticular, is asymptomatic and therefore under-diagnosed.[4]

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The onset of disease occurs between 30 and 60 years of age (middle-age,mean age: 50 years).[1-5,13,15,16] Children are rarely affected.[2,3,15,16] Women are affected more (twice as) commonly than men.[1,3-5,8-10,13,15-17] OLP etiopathogenesis is complex and presumably dependent on the interaction of different factors.[1] Several cell types, proteins of the extracellular matrix and chemokines, contribute to the onset of the OLP through the activation of different pathways.[1,17] The presence of cells that involve migration and activation of T-cells and killing of keratinocytes produce an antigen-specific cell-mediated immune response, however, the performance of matrix metalloproteinases, chemokines and mast cell are responsible for a nonspecific immune response.[1,2,5,9,17] However, OLP appears to be a T-cell-mediated auto immune disease.[2,4,7,16-18] Evidence points out that the disease is an immunological process triggered by an antigen that alters the basal keratinocytes of the oral mucosa making them susceptible to cell immune response. It induces the activation of CD4+T and CD8+T lymphocytes and cytokines such as interleukin-2, interferon gamma (IFN-γ) and tumor necrosis factor which determine the keratinocytes apoptosis.[1,3,4,16,17] Despite the extensive literature regarding the OLP origin and development mechanism, its etiology remains uncertain, and the pathogenesis is still the object of much speculation. One believes that different external agents, especially virus and trauma and internal agents, like stress and the heat shock protein (HSP) antigen expression, can trigger OLP.[1,3,4,9] OLP also develops in sites of trauma (Koebner phenomenon) and can be exacerbated by mechanical factors including biting/chewing habits, dental procedures and rubbing of malpositioned or ill-fitting dental appliances (i.e., dentures, partials and mouth guards). Heat and irritants from tobacco smoking may also aggravate lesions.[4,9] With respect to the antigen of intrinsic origin, the HSP stands out, expressed by all cell types, and functions essentially for cell communication, differentiation and growth, signal transduction and apoptosis. The increase in this protein expression can occur in response to several exogenous agents, such as temperature change, medications, viruses, nutrients deprivation and growth factors.[1] Other etiological factors believed to be associated with OLP include genetic predisposition, diabetes, hypertension and infections.[1,3,4]

OLP lesions commonly present as asymptomatic white striae (Wickham's striae) with a bilateral symmetrical distribution, predominantly on the buccal mucosa along the occlusal line.[1,3-5,8,9,14-17,19] OLP most commonly involves the buccal mucosa (upto 90%), gingiva and tongue.[4,5,8-10] Less common sites include the palate, lip and floor of the mouth.[4,5] Unilateral presentation of OLP is atypical.[4] LP has a wide range of clinical appearances that correlate well with disease severity.[2] Andreason described six clinical variants of OLP.[1,3-5,8-10,15,16] They are as follows:

- Reticular: Reticular LP has a distinct and characteristic clinical appearance of thin, slightly raised white lines that connect in a pattern resembling lacework, reticular or annular appearance. This arcuate pattern of white lines can be on erythematous or non erythematous mucosa and is referred to as Wickham's striae. The most common location for reticular LP is the buccal mucosa, followed by the buccal vestibule, tongue, gingiva and labia. Reticular LP commonly occurs bilaterally[2-5]
- Plaque-like: Plaque-like LP appears as a slightly raised or flat white area on the oral mucous membranes. It cannot be rubbed off and is indistinguishable from other focal leukoplakias. The most common location for plaque-like LP is the tongue and more than one location can be involved[2,4,5,14]
- Erosive/atrophic/erythematous: Erosive LP most often appears as a mixture of intensely erythematous mucosa with large areas of irregularly shaped ulceration with a whitish-yellow pseudomembrane. The degree of atrophy, erythema and central ulceration can vary from lesion to lesion.[2] Erythematous and erosive OLP is almost always accompanied by reticular white papules/striae on its periphery, a clinical clue that facilitates diagnosis.[4,17] The erosive form, although less frequent, are usually symptomatic, ranging from slight discomfort to episodes of intense pain[1,9,16]
- Papular: Small, white, raised papules
- Ulcerative: Ulcers are often but not always within white areas
- Bullous: Manifesting as small vesicles or blisters within white areas (rarely seen).[1,3-5,8-10,15,16]

These different presentations may merge or coexist in the same patient.[2-4,9,16] Three distinct clinical presentations most often are described: Reticular, erosive and plaque-like.[2,14]

Desquamative gingivitis

Approximately, 10% of patients have disease confined to the gingiva.[2-4] Gingival involvement usually presents as desquamative gingivitis in which the gingival epithelium is easily peeled away from the underlying submucosa.[2,4,5,9,14] Erythema and erosions can cause significant pain (burning, irritation), swelling and bleeding.[2,4,5] Differential diagnosis must include other mucocutaneous disorders, such as pemphigoid and pemphigus, requiring direct immunofluorescence (DIF) examination in addition to histopathological evaluation for diagnosis.[2-5,14]

Vulvo–vaginal-gingival syndrome

LP often affects the genitalia. Approximately, 20–25% of women with OLP have vulvo-vaginal involvement.[4,13,20] The vulvo-vaginal-gingival syndrome consists of erosive or desquamative vulvitis, vaginitis and gingivitis. It was originally described in 1982 by Pelisse as a distinct subgroup of LP. Women with the vulvo-vaginal-gingival syndrome may demonstrate reticular or erosive OLP with occasional scarring resulting in vulvar destruction and vaginal stenosis.[4,20]

Oral lichen planus and lichen planus

LP commonly involves the oral mucosa, but extraoral sites may be affected including the skin, scalp, genital area and nails.[2,3,17] Forty percent lesions occur on both oral and cutaneous surfaces, 35% occur on cutaneous surfaces alone and 25% occur on mucosa alone ("isolated"OLP).[2-4,9,13,15,21]

Cutaneous LP lesions usually develop within several months of OLP lesions. There is no correlation between extent or severity of OLP and cutaneous LP.[4] Cutaneous LP lesions are typically flat-topped, purple papules with white striae called Wickham's striae. They occur most often on the arms, legs and back and are usually pruritic.[3,4,9] Generalized involvement may occur along with significant postinflammatory mucocutaneous hyperpigmentation.[4] Cutaneous LP lesions typically resolve within 1–2 years but OLP lesions may persist for more than 20 years.[1-3] OLP is chronic with periods of exacerbation and remission.[1,4,8] Stress was identified most frequently by patients as a cause of their acute disease flares.[4,8,15] OLP rarely undergoes spontaneous remission. Close follow-up and monitoring with monthly visits are necessary for patients with severe symptoms, poorly controlled erosive disease and those on systemic therapy. Once disease activity and symptoms are fairly well controlled, OLP patients should be evaluated every 6–12 months.[4]

Dubreuil was the first to describe the histopathology of OLP in 1906.[10,21] The histological features of OLP vary according to the clinical picture and are not dissimilar from those of the cutaneous form.[2,5] Although the histopathologic features of LP vary slightly among the various clinical types, three hallmark features are considered necessary for an LP diagnosis:[1-5,8,9,14,19]

- Hyperortho or hyperparakeratosis, usually with a thickening of the spinous cell layer (acanthosis) and shortened, pointed saw-toothed appearance of the rete ridges. These thickened areas are clinically seen as Wickham's striae. Between these areas, the epithelium is often atrophic with the loss of rete ridge formation[8]
- Necrosis of the basal cell layer often referred to as"liquefaction degeneration"[8,12]
- A dense subepithelial band of chronic inflammatory cells, usually T lymphocytes in the subjacent connective tissue that can transgress the basement membrane and can be seen in the basilar or parabasilar layers of the epithelium.[1-5,8-10,12,14] Scattered within the epithelium and superficial connective tissue are seen Civatte's (colloid, hyaline or cytoid) bodies which are isolated epithelial cells, shrunken with eosinophilic cytoplasm and one or multiple pyknotic nuclear fragments. These Civatte's bodies are thought to represent apoptotic keratinocytes and other necrotic epithelial components that are transported to the connective tissue for phagocytosis.[2-4,8,19,21]

Direct immunofluorescence

The tissue diagnosis of LP may be greatly aided by the use of immunofluorescence.[2] DIF studies have shown a linear pattern and intense positive fluorescence with antifibrinogen that outlined the basement membrane zone in OLP frozen sections.[2,4,16] Occasionally, specimens demonstrate IgM staining cytoid bodies in the dermal papilla or peribasilar areas. When present in large numbers or clusters, these cytoid bodies are highly suggestive of LP.[2,16] DIF can aid in distinguishing OLP from other lesions, especially vesiculobullous lesions such as pemphigus vulgaris, benign mucous membrane pemphigoid and linear IgA bullous dermatosis.[16] However, immunofluorescent studies are adjuvant and not confirmatory for the diagnosis of OLP.[14]

Protocol/algorithm for treatment

To date, no cure for OLP or its dermal counterpart exists.[2,3,17] The treatment goal is always two fold: (1) Alleviation of symptoms and (2) monitoring for dysplastic changes.[2-5,7,10,17] Small areas of the reticular or plaque-like form of LP are rarely treated unless they become symptomatic, persist or become widespread.[2,4,15] In general, treatment is instituted to patients with painful, erosive and ulcerative forms of the disease.[3,4,10,22]

A wide spectrum of topical and systemic therapies are used in its management.[3] Treatments that have been tried successfully for the palliation of symptomatic OLP include topical and systemic corticosteroids, topical tacrolimus and cyclosporine (steroid-sparing immunosuppressants) and systemic immunomodulators such as azathioprine and mycophenolate mofetil.[1,3,10,16,17,22,23] Topical corticosteroid therapy is the mainstay of treatment for the ulcerative disease.[1,3,4,6,15-17] Patients with widespread OLP, desquamative gingivitis or multiple mucocutaneous sites of disease may require systemic immunomodulatory therapy.[3,4,9,10,15,22] Intra-lesional injections of triamcinolone (10 mg/ml) in lidocaine are generally reserved for more refractory, persistent cases.[9,15,22] The multidisciplinary treatment is very important, especially in the presence of cutaneous and psychological involvement.[8] Recently, numerous reports have suggested the use of topical tacrolimus or pimecrolimus in solutions, ointment or cream form for OLP resistant to topical or systemic therapies.[2-4,15,17,22] Topical tretinoin (all transretinoic acid) has produced generally good results in patients with OLP, especially in reticular lesions.[9,15,17,22] Recently, some reports have shown aloevera to be an effective substitute for topical treatment of OLP.[7,21] The use of lycopene has shown favorable results in OLP patients.[6] Laser therapy and other recent modalities, e.g. PUVA (8-methoxypsoralen and long-wave ultraviolet A light) and photodynamic therapy are tried as the final remedy in recalcitrant OLP.[1,8,15,17,22,23]

Since the first report in 1910 of gingival cancer diagnosed in a patient with oral LP, a large number of similar cases have been published.[2,14,22,24] The frequency of malignant transformation ranges from 0% to 5.3% with the highest rate noted in erythematous and erosive lesions.[4,16,18,22,24] Malignant transformation of OLP is still controversial and further prospective studies are required.[2-4,8,9,14,16,22,24] Clinically, it is important that patients with OLP, particularly patients who have erosive and ulcerative disease, undergo biannual follow-up evaluations.[2,3,8,15,16]

ORAL LICHENOID LESION/ORAL LICHENOID REACTION

The oral mucosa also manifests LP like lesions as hyperkeratotic, white, thickened, inflammatory reactions, which are said to be "lichenoid." Various terminologies such as OLL, oral lichenoid reaction (OLR), oral lichenoid tissue reaction, lichenoid contact stomatitis and LP like lesions have been used to describe this reaction.[12]

Their etiopathogenesis is not quite clear; however, they are most commonly considered an immunopathological reaction to various etiological factors such as pharmaceuticals, graft versus host disease reaction and contact reaction to dental materials.[1,3-5,8,14,18,25] VanderWaal updated the classification of OLL, which distinguished these lesions into four types.[13,14]

- Amalgam restoration, topographically associated OLL
- Drug-related OLL
- OLL in chronic GVHD
- OLL, unclassified (e.g., erythematous changes limited to the gingiva without signs of "classic" OLP elsewhere in the oral cavity, or lesions that have an LP like aspect but that lack one or more characteristic clinical features such as a bilateral presentation).

Amalgam restoration, topographically associated oral lichenoid lesion

LP-like lesions may be linked to dental restorative materials, most commonly mercury-containing amalgam.[3,4,11,14,16,25] In 1986, Lind employed the term OLR to refer to clinical lesions related with amalgam restorations.[8,19] Other significant corrosive products in amalgam include copper and tin, which may also be a cause of lichenoid mucosal changes.[11,25] Aside from amalgam, other metals such as gold, palladium, nickel, chrome and cobalt may induce oral lichenoid mucositis.[8,11,16,25] A sensitivity response resulting in immune-mediated damage of the basal epithelium may occur secondary to contact of the oral mucosa to some dental restorative materials.[3,11] Besides dental materials, a number of topical substances including cinnamon and other flavorings, oral cosmetics, various food products and beverages along with additives may trigger an adverse reaction on the oral mucosa.[4,8,14,25]

Although OLP lesions are generally bilateral and symmetrical, those arising due to sensitivity to dental restorations have an asymmetrical and often unilateral distribution presenting adjacent to the restorations.[3,14] The key clinical information required to confirm the diagnosis of amalgam restoration is the close topographic relationship between the restoration and the lesion. Typical sites include the lateral borders of the tongue and buccal mucosa.[4,14,25]

It is impossible to differentiate between idiopathic LP and lichenoid contact allergic manifestations based solely on these histopathological criteria.[4,25] Histopathologic features which are different from OLP include the predominant formation of lymphoid follicles chiefly consisting of plasma cells and neutrophils.[14] The combination of a positive patch test and a strong clinical association between oral lichenoid contact reaction lesions and amalgam restorations is an excellent predictor of improvement following amalgam replacement.[3,4,11,22]

If a patient tests positive to any components in existing dental restorations most commonly amalgam or ammoniated mercury,then removal/replacement/coverage of the restoration in direct contact with the lesion is usually advised.[3,4,8,25] Resolution after removal confirms the diagnosis more reliably.[11,14] OLLs associated with contact hypersensitivity, especially to dental metals are a possible risk factor for the development of squamous cell carcinoma of the mouth.[25] A biopsy is recommended when lesions exhibit atypical clinical features, in the absence of a response or when there is a concern for possible malignancy.[4,13]

Drug-related oral lichenoid lesion

Lichenoid drug eruptions (LDEs) can be considered a variant of LP.[5] LDEs were first reported in 1940 in association with gold therapy for rheumatoid arthritis. In 1945, the first of a series of reports appeared implicating antimalarial drugs.[26] Drug-induced OLRs were later cited in 1971.[27] The prevalence of oral lichenoid drug reactions (OLDR) seems to be increasing, perhaps because of the realization that the entity has a cause that is distinct from idiopathic LP. The increased occurrence may also result, in part, from the introduction of numerous new categories of medications that have a greater tendency for lichenoid reactions as a side effect.[2,27]

Numerous drugs have been reported to be associated with LDE, although only some of these have been confirmed as causing oral involvement.[5,26] Most often, antibiotics, antihypertensives, gold compounds, diuretics, antimalarial agents and nonsteroidal anti-inflammatory agents are responsible for lichenoid reactions.[2-4,8,16,27] Hepatitis B vaccination has been reported to cause OLDR in pediatric patients.[4] Some authors consider it quite likely that the so-called "Grinspan syndrome," in which OLP is related to diabetes mellitus and arterial hypertension, is infact simply an example of OLR induced by the drugs simultaneously used to treat the latter two diseases.[27]

Clinically, lesions are indistinguishable from OLP, demonstrating erythematous erosions and ulceration with focal areas of radiating striae.[2,27] OLDR lesions present as white reticular papules or erythematous erosions, depending on the drug involved and can be associated with significant oral pain.[9] Oral LDEs can appear at sites atypical for OLP, such as the palate or lip and unlike OLP, lesions tend to be unilateral.[4,5,26-28]

Attempting to differentiate between the two conditions histologically may be difficult as, in common with the clinical findings, those features considered to be characteristic of an LDE can also be identified in some cases of idiopathic OLP.[5] Histological features which may favor the diagnosis of OLDR include a deep and diffuse subepithelial mixed infiltrate of lymphocytes, plasma cells and neutrophils with or without eosinophils; perivascular inflammation and intraepithelial colloid bodies.[2,4,5,14,26] The clinical suspicion of the presence of a lichenoid reaction is raised by an appropriate drug history, particularly if the patient is taking a"high-risk"drug.[5,14] The index of suspicion is enhanced by a clinically atypical distribution of lesions, including involvement of unusual and unilateral sites, and"nonclassical" (i.e.,lichenoid) histology.[5] Indirect immunofluorescence (IIF) studies of OLDR patient sera may detect circulating basal cell cytoplasmic autoantibodies in a "string of pearls" pattern. IIF is negative in OLP.[4]

Treatment of OLDR consists of discontinuation of the suspect medication and substitution with an alternate medication.[2,4,5] OLDR lesions typically resolve within weeks to months of drug cessation, but delayed responses may also occur.[2,4,14,27] Residual, milder, reticular and erosive lesions may persist.[2,4]

Oral lichenoid lesion in chronic graft versus host disease

GVHDs occur mainly in the recipients of allergic bone marrow transplantation (BMT) to treat life-threatening diseases of blood and bone marrow such as leukemia, aplastic anemia or disseminated metastatic diseases.[14,29] GVHD is a complication that occurs through the activation of T-cells in response to molecules from the major histocompatibility complex after an allogenic histocompatible BMT. Donated T-cells recognize molecules from the host tissue as foreign.[29]

Oral lesions may be associated with GVHD and are present in 25–70% of the cases.[29] Diagnosis of GVHDs is essentially clinicopathological as 85% of GVHDs elicit clinical and histopathologic features of OLP.[13,14] The LP- like lesions sometimes seen in graft-versus-host disease suggest there is an immunological basis to LP.[3]

Oral GVHD is clinically and histologically indistinguishable from oral LP.[22] Histopathologic features include epithelial maturation disturbances, with dyskeratosis, basal squamatization, subepithelial vacuolization at the stromal interface and sparse lymphocytic infiltration in the upper lamina propria. Perivascular cuffing of inflammatory cells is evident.[14]

The most interesting data on lichenoid lesions and malignancies are those from patients who underwent allogeneic BMT and developed oral GVHD. Case reports and large studies describe numerous episodes of oral cancers (mainly squamous cell carcinoma) in patients with oral GVHD.[22]

EVOLUTION OR REVOLUTION

Clinically and histologically it is not possible to distinguish OLP from OLL.[16,28] OLLs share common clinical and histological features.[1,4,28] Despite the reported differences between idiopathic LP and LDE, the WHO "gold standard" criteria for LP does not distinguish between the two conditions.[12,21,26,30]

The modified WHO diagnostic criteria of oral lichen planus and oral lichenoid lesion (2003)

Clinical criteria

- Presence of bilateral more or less symmetrical lesions
- Presence of a lace like network of slightly raised gray-white lines (reticular pattern)
- Erosive, atrophic, bullous and plaque-type lesions are accepted only as a subtype in the presence of reticular lesions elsewhere in the oral mucosa. In all other lesions that resemble OLP but do not complete the aforementioned criteria, the term "clinically compatible with" should be used.

Histopathologic criteria

- Presence of a well-defined band like zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes
- Signs of liquefaction degeneration in the basal cell layer
- Absence of epithelial dysplasia
- When the histopathologic features are less obvious, the term "histopathologically compatible with" should be used.

Final diagnosis oral lichen planus or oral lichenoid lesion

To achieve a final diagnosis, clinical as well as histopathologic criteria should be included:

OLP: A diagnosis of OLP requires fulfillment of both clinical and histopathologic criteria.

OLL: The term OLL will be used under the following conditions:

- Clinically typical of OLP but histopathologically only compatible with OLP
- Histopathologically typical of OLP but clinically only compatible with OLP

- Clinically compatible with OLP and histopathologically compatible with OLP.[30,31]

Based on the modified WHO criteria, the unilateral lesions typical of OLP would fall under the category of OLL inspite of being histopathologically typical of OLP. In addition, the clinically typical OLP lesions with signs of dysplasia will fall under the category of OLL inspite of the fact that OLP is a recognized precancerous condition/a potentially malignant disorder. This modification of the older criteria for the diagnosis of OLP and OLL has led to a group of lesions which require serious consideration before devising the line of treatment; the treatment of OLP and OLL being totally different from each other inspite of clinical and histopathological similarities. Futhermore, the malignant transformation rate of this entity will also falsely change in literature over a period of time as many lesions of OLP diagnosed as OLL as per the modified WHO criteria will show malignant transformation hence leading to a decrease in the malignant transformation of OLP and increase in the malignant transformation of OLL.[31]

OLL are distinguished from OLP by two factors: (1) The association with the administration of a drug, contact with a metal or food stuff or systemic disease and (2) their resolution when the offending agent is eliminated.[2,4] However, the differentiation is not always straight forward.[1,3,5]

The large number of patients testing negative in hypersensitivity tests may be related to the absence of corrosion products in these tests.[8] Oral lichenoid contact lesions may resolve following removal and replacement of the causative restorative material but this may take some months and cannot be guaranteed.[3,4,11,13,14,22,25] The ensuing replacement of suspect dental materials and other substances in the oral cavity is often not easy and is not always accepted by the patient.[25]

Almost all therapeutic drug groups have been associated with LDE, but the influence of drug-drug interactions has not been acknowledged. Thus, the LDE diagnosis is based on the patient's case history but is often jeopardized by simultaneous intake of multiple drugs, i.e. polypharmacy. Furthermore, it is difficult to establish a causal relation to drugs as the majority of middle-aged and older persons are exposed to drugs and polypharmacy on a daily basis for treating systemic disease.[28]

Relating the commencement of medication (or changes in dosing) to the initial onset of oral symptoms may identify etiological clues. However, there may be a lag phase between the start of medication and onset of signs and symptoms.[4,5] The resolution of lesions after removal of an offending agent may be prompt or may take months to clear.[2,27] The absence of immediate resolution does not preclude an adverse drug event as, in unusual cases (notably with gold, penicillamine and methyldopa, all potent LDE inducing agents), symptoms can persist for long periods following drug withdrawal.[5]

In the case of drug-induced OLRs, due evaluation of the risk/benefit ratio of suspending the medication is required. As has been commented, even if the causal medication can be suspended, the lesions may take several months in improving. In addition, the pharmacological treatment of OLRs is often not feasible because the long list of agents capable of causing such lesions includes many substances used to inhibit autoimmune T lymphocyte responses. These drugs are commonly used to treat very severe forms of LP in its atrophic-erosive presentation, and, in particular, include dapsone, levamisole, tetracyclines and IFN.[27]

Confirmation of a possible LDE may be achieved by the withdrawal and subsequent rechallenge using the suspect drug and then, monitoring the effects on the oral lesions.[5,26] However, such an approach is unrealistic and therefore the connection with certain drugs can be difficult to prove.[5]

CONCLUSION

The modified WHO criteria (2003) have changed the diagnostic scenario for OLP and OLL. It is difficult to comment whether it is the evolution of our knowledge for the clinical entities based on accumulated knowledge over a period of time; or a revolution leading to a conclusion that the previous studies and literature regarding these two entities had serious discrepancies. The differentiation of OLL from OLP require a thorough history and complete mucocutaneous examination in addition to specific diagnostic testing (i.e. DIF, IIF, cutaneous patch testing) for confirmation of lesion and cause because the best way to treat OLL is to identify the drug or material causing it and replace it with another drug or material.If the causative agent cannot be discontinued or if residual lesions persist after elimination of cause therapy for OLP, i.e. topical corticosteroids can be utilized with variable success for OLL depending on the extent and severity of residual disease. Above all, a more universal diagnostic criteria with inclusion of treatment guidelines are required for OLP and OLL in order to prevent the misdiagnosis and furthermore, the ensuing malignant transformation mishaps.

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