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## Drug-induced oral lichenoid reactions. A literature review

P Serrano-Sánchez <sup>1</sup>, JV Bagán <sup>2</sup>, Jiménez-Soriano <sup>3</sup>, G Sarrión <sup>1</sup>

<sup>1</sup> Dental surgeon. Postgraduate in Medicine and Oral Surgery. Faculty of Medicine and Dentistry, University of Valencia. Service of Stomatology, Valencia University General Hospital. Valencia, Spain

<sup>2</sup> DDS, PhD Chairman of Oral Medicine, University of Valencia. Head of the Service of Stomatology. Valencia University General Hospital. Valencia, Spain.

<sup>3</sup> DDS, PhD Professor of Oral Medicine. University of Valencia. Valencia. Spain.

Correspondence:  
Hospital General Universitario  
Servicio de Estomatología  
Avda. Tres Cruces s/n  
46014 - Valencia (Spain)  
dr.serranosanchez@gmail.com

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eMail: [jced@jced.es](mailto:jced@jced.es)

### Abstract

The terms oral lichenoid reactions or oral lichenoid lesions refer to lesions histologically and clinically similar to oral lichen planus, though with the particularity that in these cases the underlying cause is identifiable. In addition, these lesions are described according to the causal factor involved, including alterations resulting from direct contact with dental restoration materials, drug-related lesions, and lesions associated to graft-versus-host disease.

Drug-induced oral lichenoid reactions or oral lichenoid lesions were first cited in 1971 by Almeyda and Levantine. Since then, many drug substances have been associated with such lesions. The most common agents are nonsteroidal antiinflammatory drugs and angiotensin converting enzyme inhibitors.

**Key words:** Oral lichenoid reactions, oral lichenoid lesions, drugs, medicines, drug-induced oral lesions.

Drug groups	Drug	Reference	No. cases	Histology	
<b>Antihypertensive</b>	Methyldopa	Stevenson (1971)	1	+ ve	
	Methyldopa	Burry&Kirk (1974)	3	2 + ve 1 - ve	
	Methyldopa	Hay&Reade (1978)	17	8 + ve 2 - ve 9 no Bx	
	Methyldopa	Brooks (1982)	1	No Bx	
	Methyldopa	Williams (1983)	1	- ve	
	Oxprenolol	Wiesenfeld et al. (1982)	1	+ ve	
	Practolol	Felix et al. (1974)	1	Not clear	
	Propranolol	Hawk (1980)	1	+ ve	
	<b>Antimalarials</b>	Chloroquine	Savage (1958)	1	No Bx
		Pyrimethamine	Cutler (1980)	1	+ ve
Quinacrine		Bagby (1945)	2	+ ve	
Quinacrine		Nisbet (1945)	Many	Not registered	
Quinacrine		Schmitt et al. (1945)	16?	Mostly + ve Some no Bx	
Quinacrine		Bazemore et al. (1946)	150	None	
Quinacrine		Wilson (1946)	>300	Some + ve Some - ve Some no Bx?	
Ketoconazole		Markitziu et al. (1986)	8	+ ve	
<b>Antimicrobials</b>		Para-aminosalicylic acid	Shatin et al. (1953)	2	+ ve
		Tetracycline	Fitzpatrick (1963)	1	No Bx
	Sulfamethoxazole	Bronny&Thies (1990)	1	Not clear	
	Fenclofenac	Ferguson et al. (1984)	1	+ ve	
<b>NSAIDs</b>	Phenylbutazone	Gold (1966)	1	+ ve	
	Nonspecific NSAID	Potts et al. (1987)	27	Not clear (Mostly Bx +ve) Some - ve	
	Naproxen	Gibson et al. (1986)	1	+ ve	
	Rofecoxib	Bagán et al. (2004)	3	No Bx	
<b>Hypoglycemic drugs</b>	Tolbutamide	Hurlbut (1963)	1	No Bx	
	Chlorpropamide	Dinsdale et al. (1968)	1	+ ve	
<b>Penicillamine</b>	Penicillamine	Seehafer et al. (1981)	6	4 + ve 2 no Bx	
	Penicillamine	Powell et al. (1983)	11	7 + ve 2 - ve? 8 no Bx	
	Penicillamine	Blasberg et al. (1984)	7	+ ve	
	<b>ACEIs</b>	Captopril, Enalapril	Firth (1989)	2	Not clear
		<b>Thyrokine-selective immunosuppressors</b>	Imatinib	Pascual et al. (2006)	2
Imatinib	Ena et al. (2004)		1	+ ve	
Imatinib	Lim & Muir (2002)		1	+ ve	
<b>Miscellaneous</b>	Allopurinol	Chau et al. (1984)	3	1 + ve 2 no Bx	
	Amiphenazole	Baker et al. (1964)	4	1 + ve 1 - ve 2 no Bx	
	Amiphenazole	Dinsdale & Walker (1966)	1	+ ve	
	Carbamazepine	Roberts & Marks (1981)	1	+ ve	
	Cyanamide	Torrelo et al. (1990)	1	+ ve	
	Levamisole	Kirby et al. (1980)	2	+ ve	
	Lithium	Hogan et al. (1985)	1	+ ve	
	Lithium	Campisi et al. (2005)	1	+ ve	
	Lorazepam	Colvard et al. (1986)	1	- ve	
	Escitalopram	Aframian (2007)	1	No Bx	
	Methopromazine	Groth (1961)	1	+ ve	
	Pyritinol	Ishibashi et al. (1973)	1	+ ve	
	Clotidrogel	Guijarro (2003)	1	+ ve	
	Adalimumab	Simone et al. (2008)	1	+ ve	
	Hepatitis B vaccine	Pemberton (2000)	1	+ ve	
	Interferon-alpha 2a, rivavicin, propanolol	Armour & Lowe (2005)	1	+ ve	
	Interferon-alpha, rivavicin	Giuliani (2008)	2	+ ve	

**Table 1.** Drugs reported in the literature as being related to oral lichenoid reactions. Expanded from the study of McCartan and McCreary (4) published in 1997 (Abbreviations: Bx = biopsy; +ve = positive; -ve = negative; ACEIs= angiotensin-converting enzyme inhibitors; NSAIDs= Nonsteroidal anti-inflammatory drugs).

## Concept

The terms oral lichenoid reactions (OLRs) or oral lichenoid lesions (OLLs) refer to lesions histologically and clinically similar to oral lichen planus (OLP), though with the particularity that in these cases the underlying cause is identifiable (1).

The literature uses a range of different terms in reference to lesions of this kind (2). Most of the publications refer to them according to the causal factor involved, including alterations resulting from direct contact with dental restoration materials, drug-related lesions, and lesions associated to graft-versus-host disease (1,2).

Drug-induced oral lichenoid reactions were first mentioned in 1929, and were later cited in 1971 by Almeida and Levantine (3). Many cases were documented among United States military personnel during the war in the Pacific, southeastern Europe and Indonesia. The mentioned authors reported an apparent relationship between the clinical findings in these individuals and the prophylactic use of antimalarial drugs. Since then, many drug substances have been associated with such lesions (4).

## Epidemiology

The precise epidemiological characteristics of these lesions are difficult to establish, due to the diverse and imprecise terminology used in establishing a final diagnosis of lichen planus (LP) as “probable”, “possible” or “suggestive”, in those situations where the histopathological and clinical findings are less clear than in classical lichen planus (2). In addition, the absence of histological confirmation in most of the articles published on OLP-related disorders makes it difficult to establish their true prevalence or incidence (5).

Nevertheless, it is believed that the prevalence of OLRs attributable to drug substances is increasing. According to some authors (6), newly marketed drugs that are generally used among the population, such as antihypertensive agents, can cause such lesions as side effects. In contrast, other investigators point to increased experience and awareness among the different health professionals (dentists as well as dermatologists) as the factor contributing to improved differentiation of the broad range of disorders related to lichen planus.

## Etiopathogenesis

The etiopathogenic mechanism by which these lesions are produced is not known. The literature has identified a series of triggering factors, such as dental restoration materials, graft-versus-host disease, and a broad range of drugs (6,7).

A great many materials commonly used in restoration treatments in the oral cavity have been identified as triggering elements, including silver amalgam, gold, cobalt, palladium, chromium and even non-metals such as

epoxy resins (composite) (1,7,8).

Bäckman and Jontell (9) in turn have pointed to dental material coadjuvants such as dental tartar deposited upon the materials, oral breathing and hyposialia as etiological factors. These authors published the case of a patient with all three factors who developed a lichenoid reaction in the absence of dental restoration.

On the other hand, many drug substances are reportedly able to produce such reactions (Table 1). The most commonly implicated agents are nonsteroidal antiinflammatory drugs and angiotensin converting enzyme inhibitors (10, 11).

In many cases these drugs are used in combination – thus suggesting the possible existence of synergic effects between them. Some authors consider it quite likely that the so-called “Grinspan syndrome”, in which oral lichen planus is related to diabetes mellitus and arterial hypertension, is in fact simply an example of oral lichenoid reaction induced by the drugs simultaneously used to treat the latter two diseases (12).

## Clinical manifestations

The clinical manifestations of oral lichenoid lesions (Fig. 1) are indistinguishable from those of oral lichen planus (7) – with mainly erythematous erosive lesions and an important ulcerative component. All these lesions are characterized by the presence of whitish streaks known as Wickham striae, similar to those seen in lichen planus (13). However, a very significant distinguishing factor with respect to OLP is their atypical location, and particularly the absence of bilaterality of the manifestations (2-6,9,13).



*Fig. 1. Image of a unilateral lichenoid reaction affecting the right cheek mucosa in a patient subjected to antihypertensive drug treatment.*

In relation to drug-induced lichenoid reactions, no specific clinical features have been described capable of firmly differentiating them from lichenoid reactions caused by other factors. The only clue in this sense is an antecedent of recent or chronic exposure to some drug



**Fig. 2.** Image of a unilateral lichenoid reaction affecting the left cheek mucosa in direct relation to a ceramometallic crown.

substance. As a result, a differential diagnosis must be established, considering cases associated to the use of dental materials (Fig. 2), where the lesions are found in contact with or very close to the restorative materials, and confirming that the patient has no antecedents of graft-versus-host disease (6,7,14).

**Diagnosis**

The diagnosis of OLRs is based on their clinical charac-

teristics and the histological findings (9,15). However, the sensitivity and specificity of histological diagnosis are very low (4). In addition, no definitive molecular diagnostic markers have been established to date (16). Van der Meij et al. (6) have proposed a modification of the diagnostic criteria of the World Health Organization for oral lichen planus and lichenoid reactions (Table 2). As these are cause – effect lesions, the most precise diagnostic clue is determination of whether or not the lesions disappear after eliminating exposure to the suspect etiological factor (8).

However, in the case of drug-induced lesions, suspension of the medication may place patient health at risk (13). Furthermore, in many cases such measures are not useful and reliable as a diagnostic strategy, since the lesions may take months in resolving after suspending the suspect medication (3,17).

**Treatment**

The management of such lesions first requires identification of the triggering factor, and the elimination of exposure to it.

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

<b>Diagnostic criteria for oral lichen planus (OLP) and oral lichenoid lesions (OLLs)</b>
<p><b><u>Clinical criteria:</u></b></p> <ul style="list-style-type: none"> <li>▪ Bilateral presentation, more or less symmetrical lesions</li> <li>▪ Presence of white striae (reticular pattern)</li> <li>▪ Erosive, atrophic, bullous or plaque manifestations are only accepted as subtypes when always accompanied by reticular lesions located anywhere in the mucosa.</li> </ul> <p>The term “clinically compatible with” is to be used with all lesions similar to oral lichen planus that do not meet the mentioned criteria.</p>
<p><b><u>Histological criteria:</u></b></p> <ul style="list-style-type: none"> <li>▪ Well defined, mainly lymphocytic band infiltration in the most superficial zone of the connective tissue.</li> <li>▪ Signs of degenerative liquefaction in epithelial basal layer.</li> <li>▪ Absence of epithelial dysplasia.</li> </ul> <p>The term “histologically compatible with” is to be used in application to all histopathological findings less clearly compliant with the mentioned criteria.</p>
<p><b><u>Final diagnosis of oral lichen planus and oral lichenoid lesions:</u></b></p> <p>The clinical and histopathological criteria must be included in order to establish a final diagnosis. Both the clinical and histopathological criteria must be met in order to diagnose oral lichen planus. The term oral lichenoid lesions is to be used under the following conditions:</p> <ol style="list-style-type: none"> <li>(1) Clinically characteristic of oral lichen planus but histologically only “compatible with” oral lichen planus</li> <li>(2) Histologically characteristic of oral lichen planus but clinically only “compatible with” oral lichen planus</li> <li>(3) Both clinically and histologically “compatible with” oral lichen planus.</li> </ol>

**Table 2.** Modified World Health Organization criteria for the diagnosis of oral lichenoid reactions (OLRs), oral lichenoid lesions (OLLs) and oral lichen planus (OLP). Van de Meij et al. (6), 2007.

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 lymphocytes responses. These drugs are commonly used to treat very severe forms of lichen planus in its atrophic – erosive presentation, and in particular include dapsone, levamisole, tetracyclines and interferon (18,19).

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