

ORAL LICHEN PLANUS AND ORAL LICHENOID REACTION – AN UPDATE

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SUMMARY – Oral lichen planus (OLP) and oral lichenoid reaction (OLR) are clinically and histopathologically similar diseases. Whereas OLP is a consequence of T cell mediated autoinflammatory process to a still unknown antigen, OLR might be caused by drugs, dental restorative materials and dental plaque. Pubmed was searched and 24 publications published over the last three years regarding etiology, diagnosis and malignant alteration were included in this study. Patients with OLR who have amalgam fillings near lesions should have them replaced, i.e. when possible they should be referred to patch test, as well as when drug-induced OLR are suspected. OLR lesions induced by drugs should disappear when the offending drug has been discontinued. Histology finding in OLR consists of more eosinophils, plasma cells and granulocytes in comparison to OLP lesions. Furthermore, OLP lesions showed more p53, bcl-2 and COX-2 positivity when compared to OLR. OLP is characterized by infiltration, atrophic epithelium, rete pegs and Max Joseph spaces, while deep infiltration into connective tissue and hyperkeratosis were the criteria for making the diagnosis of OLR. The number of degranulated mastocytes in the reticular layer, as well as the number of capillaries was higher in OLR in comparison to OLP. It seems that OLR are more prone to malignant alteration in comparison to OLP.

Key words: Lichen planus, oral; Mouth diseases; Lichenoid eruption

Introduction

Oral lichen planus (OLP) is a relatively common chronic inflammatory disease the etiopathogenesis of which is not fully known. Several factors have been proposed in an effort to explain the variety of clinical manifestations and periods of exacerbation and remission that are typical for this disease^{1,2}. In most

cases, OLP occurs bilaterally, as opposed to oral lichenoid reaction (OLR), which is generally unilateral. Differentiating OLP and OLR may be difficult based on clinical symptoms and often based on histologic findings too. OLP is a disease of unknown etiology, mediated by T cells, to a still unknown antigen. Unlike OLP, OLR are often associated with a known etiologic factor such as reactions to dental materials, drugs and plaque³. Although OLR are clinically and histologically similar to OLP, recent literature data show that there are clear differences between these two entities. The aim of this paper is to review the literature on Pubmed regarding OLP and OLR over the last three years.

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Materials and Methods

PubMed was searched to determine whether there were new publications in the last three years regarding distinction in the etiology, diagnosis and therapy of malignant alteration between OLP and OLR. Twenty-four papers available on PubMed were included in this review.

Results and Discussion

Oral lichen planus and OLR are clinically and histologically similar lesions with different treatment planning and prognosis. However, recent research indicates that it is possible to differentiate these two lesions with additional tests.

Difference in the diagnosis of oral lichen planus and oral lichenoid reaction based on histopathologic findings

Kamath *et al.*⁴ had thoroughly searched medical and dental databases including PubMed, Ovid, Cochrane, Pubget, and Researchgate, and found that OLR are often unrecognized and most of the cases categorized as OLP. Suter and Warnakulasuriya⁵ evaluated patients who had OLR, oral lichen resistant to treatment and atypical lichenoid changes over a 10-year follow up period. All patients underwent skin patch testing and all those who tested positive were advised to change their filling material. Out of 115 patients, 67.8% tested positive for dental materials and around one-quarter of them tested positive for mercury or amalgam. There was no correlation between pathologic findings and patch test. Moderate to complete remission was found in 81% of 26 people with positive patch test in whom amalgams were replaced. The same authors⁵ conclude that patch test is a valuable tool in diagnosing OLR. Arreaza *et al.*⁶ compared the expression of p53 protein in OLP and OLR in 65 patients, 31 with OLP and 34 with OLR. Results of the same study⁶ showed that there were more p53 positive cases in OLP patients as compared to people with OLR. However, the difference was not statistically significant. Mravak-Stipetić *et al.*⁷ conducted a retrospective study on 92 patients with OLP and 14 patients with OLR whose diag-

nosis was verified by histopathology in 52.2% and 42.9% of cases, respectively. Histologically, there were significantly more eosinophils, plasma cells and granulocytes established in OLR lesions compared to OLP. The same authors⁷ conclude that the type of cells of mononuclear infiltrate should be defined on histopathology in order to distinguish these two states. Czerninski *et al.*⁸ analyzed 235 patients, 54% of them non-smokers and 25% current smokers. The OLP group (n=79) had more often bilateral lesions as compared with the group with lichenoid dysplasia (n=30) (70% *vs.* 40.7%) and younger age (56 *vs.* 62 years). All other parameters were comparable. Compared with OLP group, lichenoid dysplasia group consisted of more men. Since the clinical features of lichenoid dysplasia were more similar to OLP and OLR, these findings may indicate that lichenoid dysplasia is part of a spectrum of lichen planus and not an independent entity. Casparis *et al.*⁹ analyzed 692 biopsies from 542 patients (207 [38.2%] male and 335 [61.8%] female). Sex and smoking were significantly associated with the severity of the diagnosis. Mucosal lesions that were ulcerative and those that were located at the bottom of the mouth showed a higher degree of dysplasia or were diagnosed as oral squamous cell carcinoma. Smoking and joint disease were significant risk factors. Tretinoin treatment at various concentrations (0.005%-0.02%) significantly improved the diagnosis. Twelve patients (8 women and 4 men) had malignant alteration to oral squamous cell carcinoma within the mean period of 1.58 years. Malignant transformation was more common in OLR (4.4%) as compared with OLP (1.2%).

If the first biopsy showed intraepithelial neoplasia, the risk of squamous cell carcinoma had increased. Mårell *et al.*¹⁰ defined prognosis and evaluated regression of lichenoid contact lesions and OLP after replacing dental restorative materials suspected to have caused these lesions. Forty-four patients were examined six years after the first visit. After dental materials had been replaced, regression of oral lesions was significantly higher in patients with OLR as compared with the lesions of OLP patients. As there was no oral lichen lesion regression after replacing the material, it is necessary to establish the correct diagnosis, so that patients with oral lichen do not undergo unnecessary filling change¹⁰. Arreaza *et al.*¹¹ found the expression

of Bcl-2 and COX-2 to be higher in OLP than in OLR samples. Aminzadeh *et al.*¹² analyzed data from 232 patients with OLP and OLR during the 2000-2010 period. The authors¹² conclude that involvement of the lips was the only clinically significant difference between these two diseases and that people with OLR often have involvement of the lips. Infiltration, atrophic epithelium, "saw-tooth" rete pegs and Max Joseph area were histopathologically reliable criteria for distinguishing OLP, while deep infiltration of the connective tissue and hyperparakeratosis were the criteria for the diagnosis of OLR. Reddy *et al.*¹³ showed a significant increase in the number of mast cells in OLP and OLR compared to the normal mucosa and a significant increase in intact subepithelial mast cells in the inflammatory infiltrate in OLP as compared to OLR. Furthermore, they also showed a significant increase in degranulated mast cells, number of capillaries and number of eosinophils in OLR as compared with OLP. Gueiros *et al.*¹⁴ found a higher density of CD1a (+) cells in 36 patients with OLP and OLR as compared with controls, and also found the higher density of CD1a to be linked to a thin layer of inflammatory cells. Yuan *et al.*¹⁵ concluded that the number of degranulated mast cells in the reticular layer of the corium was higher in OLR as compared to OLP. This indicates that despite the increase in the number of these cells, their role is not the same in the pathogenesis of the disease. Furthermore, epithelial thickness is smaller in OLP lesions as compared to OLR. However, the difference in the thickness of basal membrane is not a reliable criterion.

Difference in the etiology of occurrence of oral lichen planus and oral lichenoid reactions

Drugs

Traditionally, OLR are related to the administration of nonsteroidal anti-inflammatory drugs and antihypertensive drugs (beta-blockers, angiotensin-converting enzyme inhibitors and diuretics, in particular hydrochlorothiazide). OLR was described in patients receiving drugs with an active thiol group, such as piroxicam, sulfasalazine, tolbutamide and glipizide. Furthermore, OLR has been associated with the following medications: antifungals (keto-

conazole), antiepileptics (carbamazepine), immunomodulatory drugs (gold salts and penicillamine), allopurinol, lithium, imatinib, infliximab, certolizumab, adalimumab, obinutuzumab, etanercept, abatacept, antituberculous drugs, duloxetine hydrochloride and topical imiquimod. Lichenoid skin reactions including involvement of the mucosa after the administration of 3-hydroxy-3-methylglutaryl-coenzyme A inhibitors such as pravastatin, which may lead to OLR together with consistent histopathology, are probably sufficient for the diagnosis of OLR caused by drugs, although the presence of circulating cytoplasmic autoantibodies in the basal layer can be better substantiated¹⁶.

Restorative materials

Muris *et al.*¹⁷ tested 906 patients, of which 24.3% reacted to palladium and 25.2% to nickel. The sensitivity to palladium, in contrast to the sensitivity to both metals, was associated with the exposure to dental crowns, metal skin reactions, OLR, dry mouth and metallic taste. After removal of the amalgam, Lynch *et al.*¹⁸ tested responses to skin patching in 31 patients with OLR. Ten (32%) patients were positive for mercury and in 8 of them amalgam was replaced, which resulted in complete or partial resolution of lesions. The same authors suggest removal of amalgam in people with positive patch test. Montebugnoli *et al.*¹⁹ showed that, after amalgam removal, complete disappearance of lesions failed to occur in 14 (22%) patients, which was significantly associated with lesion topography and positive patch test. Complete histologic healing occurred in only 7 cases (50% of patients healed clinically), but was significantly associated with a combination of positive patch test and direct contact to amalgam. Contact to amalgam and positive patch test are good but not absolute indicators of the benefit of amalgam removal. In addition, complete clinical healing does not necessarily mean disappearance of the histologic characteristics of OLP and OLR¹⁹. Lartitegui-Sebastián *et al.*²⁰ performed a prospective study on 100 people who had amalgam and underwent patch testing. OLR were established in 7 patients whose lesions were bilateral and asymmetrical and who had asymptomatic white papules and macula. The lesions were located near old and corroded amalgam fillings, and patch test was posi-

tive in two people. Amalgam removal resulted in improvement in 5 patients. Sugiyama *et al.*²¹ found typical elements of dental materials in OLR lesions, while they were not present in OLP and were negative in control samples. These elements were presumed to be parts of dental materials which had entered mucosa during erosion. For this reason, the authors suggest differentiating OLR and OLP based on the analysis of elements on biopsy²¹.

Chewing betel

Reichart and Warnakulasuriya²² found OLR caused by betel (its main carcinogen is areca nut), which is used by about 600 million people, mainly in Asia, and by people who emigrated from Asia to other countries.

Malignant alteration

Determination of the potential malignant alteration in people with OLP is complicated by difficulties in the diagnosis of OLP, in differentiating OLP from OLR, by the phenomenon that premalignant lesions may show lichenoid characteristics.

Fitzpatrick *et al.*²³ searched PubMed, Embase and Thomson Reuters Web of Science, and included 16 studies on 7806 patients with OLP, 85 of which developed oral cancer. Out of 125 patients with OLR, 4 developed oral cancer. The overall rate of malignant alteration was 1.09% for OLP, and in one study 3.2% for OLR. The mean age of patients diagnosed with cancer was 60.8 years, and it occurred more often in women and on the tongue. The mean time elapsed from OLP or OLR diagnosis to oral cancer development was 51.4 months. Mares *et al.*²⁴ analyzed 32 patients (8 with OLP and 24 with OLR) followed-up for 164 months after initial visit. Patients with OLP did not develop oral cancer, while two patients from the OLR group developed oral cancer after 45 and 143 months of follow up.

Conclusion

It seems that OLR are more prone to malignant alteration in comparison to OLP. Furthermore, it seems that histopathology reveals clear differences between OLP and OLR.

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Sažetak

ORALNI LIHEN PLANUS I ORALNA LIHENOIDNA REAKCIJA – NOVOSTI

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Oralni lihen planus (OLP) i oralna lihenoidna reakcija (OLR) su dvije klinički i patohistološki slične bolesti. OLP je posljedica autoimunog procesa koji je posredovan T limfocitima na još uvijek nepoznati antigen, a OLR može biti uzrokovana lijekovima, dentalnim materijalima i dentalnim plakom. Cilj je ovoga preglednog rada bio istražiti Pubmed te su uključena 24 rada koja su publicirana u posljednje tri godine, a s obzirom na etiologiju, dijagnostiku i malignu alteraciju ovih bolesti. Oboljeli od OLR koji u blizini lezija imaju amalgame trebaju ih zamijeniti kompozitnim ispunima, odnosno kad je moguće treba ih uputiti na *patch* test, kao i onda kada se sumnja da je OLR uzrokovana lijekovima. OLR uzrokovane lijekovima trebale bi se povući kada osoba prestane uzimati suspektni lijek. Patohistološki nalaz u OLR se sastoji od više eozinofila, plazma stanica i granulocita u usporedbi s lezijama kod OLP. Nadalje, lezije OLP imaju više pozitivnih nalaza p53, bcl-2 i COX-2 u usporedbi s lezijama OLR. OLP obilježava infiltracija, atrofični epitel, zupci pile i Max Josephovi prostori, dok OLR karakterizira dublja infiltracija u vezivno tkivo i hiperkeratoza. Broj degranuliranih mastocita u retikularnom sloju, kao i broj kapilara je veći u OLR u usporedbi s OLP. Čini se kako su OLR sklonije malignoj alteraciji u odnosu na OLP.

Ključne riječi: *Liben planus, oralni; Oralne bolesti; Libenoidna erupcija*