Oral Lichen Ruber - I
Etiology and Pathogenesis

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Summary

Oral lichen rubber (OLR) is a frequentchronic mucocutane autoimmune disease in the population. OLR mostly affects middleaged and older individuals. Women make 2/3 of patients. Etiology of the disease is still unexplained, with numerous etiologic factors being the possible cause of the onset of this disease. Genetic predispositions are the most frequently quoted cause together with the local use of specific dental materials, systematic use of specific drugs in basic disease therapy, infection, results of autoimmune disease, and disorders such as diabetes mellitus, chronic liver disease, hypertension, and emotional stress.

All the above mentioned factors can induce a sequence of immunologic events and reflect on the immunological state of the patient.Thus, induced sequence of immunological events is based on cell mediated immunity, including interactivity of oral epithelium cells and the immunological cell mediated by activity of adhesion molecules, and is behind the pathogenetic mechanism of OLR.

Key words: *oral lichen ruber, etiologic factors, pathogenetic mechanisms.*

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Introduction

From the historical standpoint Lichen ruber is early discovered disease, described in E. Wilson's article "On Lichen planus", 1869, as a special medical entity. In his article, Wilson reported that among 50 people with lichen skin lesions, in 3 patients this disorder was observed and described in the mouth, and he called it the lichen planus mucosa. The basic histopathological characteristics of lichen ruber were defined by J. Darier, 1909, and Wickham has described characteristic lines and striae on the lesion surface showing the common picture of lichen ruber (1).

For this frequent skin disease it can be said that it is a plurimucosis disease since the pathological changes, beside oral mucous membrane, can affect the esophagus, the stomach and cervix (2).

The lichen ruber occurs among all races with skin lichen ruber prevalence of 0.9 to 1.2% (3, 4), and oral lichen ruber prevalence of 0.1 to 2.2% (5).

Many studies have revealed the appearance of skin lesions together with oral manifestations, and oral disease without skin lesions have occurred in 30 to 70% of cases (5, 6, and 7).

Although there are reported cases of lichen ruber among children and younger individuals, oral lichen primarily affects middle-aged and older individuals, with 60 to 65% women (8, 9).

Clinical characteristics of OLR

Oral lichen ruber (OLR) is a chronic, mucocutane autoimmune disorder frequently noticed on the mucous membrane of the oral cavity.

In contrast to skin lesions, oral lesions last longer and have a chronic course. Oral lesions last approximately four and a half years longer than skin lesion (10), and some studies even note eight times more frequent occurrence of oral lichen compared to the skin lichen (9, 10).

Manifestations of lesions in oral lichen ruber contrary to manifestations of skin LR lesions have more forms of appearance. Recognition is not always easy because of different clinical manifestations and similarity with other hiperkeratinized lesions on oral mucous membrane. OLR usually appears on a few areas in the oral cavity. The changes mostly include the mucous membrane of the cheek and tongue, with very rare occurrence in the hyoid area and gingiva (gums). There are different classifications of OLR based on the multiplicity of morphologic changes on oral mucous membrane (11, 12).

The simplest classification proposed by Andreasen (13) distinguishes OLR based on the manifestation point of the pathological lesion in respect to the oral mucous membrane level:

- lichen ruber planus
- lichen ruber bullosus
- lichen ruber erosive

Each group in this basic OLR classification is a separate entity based on its multiplicity of morphologic changes as an integrity defect of oral mucous membrane, and could be subdivided.

The *papular form* appears on erythematous, inflammatory changed oral mucous membrane, in the shape of characteristic whitish, elevated papules, approximately 0.5 to 1 mm in size. Slightly elevated, soft, whitish striations (Wickham striae) constitute a small papule that represents hiperkeratinized epithelial areas, and have *reticular form*. This is the most common form of oral lichen found on cheek mucous membrane, vestibular and tongue mucous membrane, although it can occur on other areas of oral mucous membrane.

Continuity of characteristic stratum similar to leucoplacia has a *plaque-like form*, most frequently found on the mucosa of tongue dorsum and gingiva (gums). *Annular form* is a result of papules joining together or expanding reticular structure with a slightly atrophic lesion center. This shape originates on mucous membrane of the dorsum of the tongue resulting in the loss of papilla. Inflammatory and atrophic lesion surrounded by the papules, or the net, makes the *atrophic form* of OLR that often transforms into ulcerous form.

Lichen bullosus is rare, with only 2% of patients having a bullous lesion that persists in the mouth.

Erosive form manifests itself in mucous membrane redness and deep erosion. Such mucous membrane defect is characterized with the loss of upper layers of epithelium, transforming into an ulcerous form with their deepening. This OLR form is characterized by loss of epithelium, part of the basal membrane and the connective tissue in he lesion area. Deeper in the connecting tissue is an inflammatory reaction; such mucous membrane defects are covered with white-yellowish fibrinoid exudate. Mouth functions cause painful lesions.

Andreasen (14) reported spontaneous healing of lesions in 41% of patients with the reticular form, in contrast to the atrophic form where spontaneous healing was observed in 12% patients.

Clinical investigations of particular oral lichen forms representation reveal different results. According to Silverman (15), 46% patients show erosive form of disease, 32% patients show reticular form and 22% patients show atrophic form. In contrast, Thorna (16) reports 71% patients with reticular form, 2% with papular form, 37% with plaque-like form, 5% erosive and 33% atrophic form. More than 100% in the tested group, these results are the consequence of the synchronous representation of specific clinical forms of OLR.

Local histological characteristics of OLR

The histopathological characteristics of OLR are characteristic, although there can be some difficulties in distinguishing the OLR from lichenoide lesions, leucoplacia, lupus erythematodes (17), lichen sclerosus (18) and chronic ulcerous stomatitis (19). In spite of the characteristic clinical manifestation

of OLR, it is necessary to collect samples from oral mucous membrane, through biopsy and make an accurate diagnosis by histochemical and immunofluorescent methods (20, 21).

1906, Dubrenwill proposed the first description of OLR histological manifestation. Hyperkeratosis and ortokeratose together with granular layer edema constitute the classical OLR histological manifestation, with clinical manifestations in the form of Wickham striae, acanthosis with intracellular edema, epithelial extensions similar to saw-cogs, vacuolar degeneration of basal cellular layer, and ribbon like subepithelial cellular infiltrate in lamina propria (22).

Cellular characteristics at the beginning of pathological events reveal an enlarged number of Langerhans cells. Firmly limited, inflammatory, ribbon-like cellular infiltrate, mainly consisting of lymphocytes, growing in the subepithelial layer. The infiltrate is localized in the subepithelial layer in reticular OLR form, and in erosive form, the infiltrate protrudes deep into connective tissue (23).

The liquefaction degeneration of the basal cellular layer and appearance of eosinophilic inflammatory material below the basal membrane occur after the forming of the inflammatory infiltrate. Occasional colloid bodies are observed, e.g. dead cells of the basal layer. These are formed in the unique process of apoptosis. The cells change into filamentous bodies - "Civatte bodies", observable in the lower epithelium layers, and sometimes in the upper layers of connective tissue. In contrast to necroses, apoptosis provokes slight inflammatory reaction, and thus these cells are called non-keratinized cells in the process of apoptosis. (24).

Oral lichen ruber as a precancerous lesion

According to WHO criteria, OLR is included in the precancerous lesions of the oral cavity (25), looking for more attention in treatment of this disease.

Many authors found frequent malignant potential of oral lichen lesions although they differ in frequency of this malignant transformation, between 0.3 to 10% (26, 27, 28, and 29).

Some investigators found frequent malignancies in some OLR forms, as atrophic, erosive and ulcerous lesions (30, 31).

Relation to squamous cancer occurrence in OLR lesions (32) was also researched, and is approved by the latest studies based on noticing positive expression of the c-erb B2 protooncogene in keratinocytes (33).

Etiology and pathogenesis

Etiology of oral lichen ruber (OLR) is still unexplained because the interplay of numerous factors may have a crucial role. Cellular mediated immunity motivated by endogenous and exogenous influences have a special place in the OLR pathogenesis, especially in people with genetic predisposition for genesis of this disease.

In the OLR induction phase, various factors, regardless of their nature, linked to keratinocytes of the oral mucous membrane epithelium, regardless of weather are chemical substances, components of specific drug or numerous microorganisms. These changed keratinocytes are then induced to excrete cytokine, adhesion molecules and chemotactic substances responsible for inflammation. At this inflammation stage, excretion of tumor necrosis factor alpha (TNF-alpha), gamma-interferon (IFN-γ) and activation of keratinocytes, lymphocyte and antigen presenting dendritic cells can induce the executive stage of this disease (23, 24).

Etiology of OLR

Genetic factors

Investigations of the inheritable factors influencing the onset of this disease mainly include cases of skin lichen ruber (LR). Although this LR form is observed in single members of one family, authors have not suggested genetic predisposition as a primary etiologic factor. Thus, genetic testing (35) revealed theappearance of HLA-A3 (major tissular compatibility system antigen) in 54% examined with LR. The appearances of other antigens as the HLA-B7 were found in family LR, but the research included only a small number of patients. The authors (36) observed magnified frequency of HLA-A3, A8, B5, B8 antigen in people with OLR. In a

Chinese population with LR the growth of HLA-DR9 antigen have been observed (37). In contrast, results obtained from Caucasian people have not proved the connection between HLA I and HLA II antigen and the onset of this disease (38).

Research on HLA antigen and conceivable genetic predispositions to OLR onset among the Croatian population showed that HLA antigens: Aw19, A28, B15, B18, HLA-DR3 and HLA-DR4 can be a potential cause of this disease (39-41).

Dental materials

The connection between the onset of disease and dental materials, e.g. filling on dental tissues, were not observed in most people with OLR (42). However, closeness of dental filling or its contact with the oral mucous membrane, regardless of weather it is amalgam or some other material, may be able to cause socalled lichenoide reaction - lesions with clinical and histological similarity to OLR. This reaction is allergic or toxic counteraction to the specific components of dental materials (43).

These lesions are more expressive where other materials have been added to amalgam (44-48). These are most frequently mercury salts. People with OLR exhibit positive skin tests to mercury salts (44). Other authors, however, did not obtain similar results (42). In his study (49), Skoglund found positive skin test to mercury in 39.6% people with OLR. In 94.7% of cases with positive skin test, the withdrawal of oral lesions was observed after the amalgam filling has been replaced by other dental materials.

Oral lesions potentially related to other dental materials such as cobalt chloride have also been described (50, 51).

Drugs

It is presumed today that drugs are not connected with the appearance of oral lichen, but with lichenoide reactions that are hard to distinguish from classical OLR appearance.

The appearance of pathological oral lesions similar to OLR was observed in World War II during treatment with antimalaric drug (52).

Penneys (52) describes such pathological changes of oral mucous membrane that could be induced by many drugs, with special attention paid to gold preparations. Gold salts could induce mucocutaneus lesions, where the first and observable changes are oral lichenoide changes (53-56).

During the research of such appearances it was observed that synchronous combination of particular drugs, e.g. nonsteroid anti-inflammatory drugs and the angiotenzin-converting enzyme inhibitors can provoke the occurrence of oral lesions similar to OLR (55, 56).

A number of drugs are related with the occurrence of lichenoide changes including thiazides, diuretics, penicilamin, beta-blockers, salicylic acid, phenothiazine, lithium, lorasepam, ketoconasol, streptomycin, levamisole (57, 58).

Observation of pathological changes on the mucous membrane of oral cavity similar to OLR is based on subjective evaluation of clinicians, although some authors refer to the possibility of unilateral, erosive lesion induced by drug use (50, 54, and 59).

Infection

OLR is often linked with the influence of numerous microorganisms as gram negative anaerobe bacilli and spirochetes, although these observations are not entirely explained (60).

Occurrence of OLR has been observed in people with chronic inflammation of the gallbladder (61) and intestinal amebae infection, and local oral irritation with dental plaque flora could not be excluded (63).

OLR could be linked to existing infection caused by the fungus Candida albicans, particularly since regression of OLR occurs after antimicotic therapy (64).

Scully and El-Kom (1) observed the importance of viral antigen in the incidence of OLR.

This disease has been described in the composition of HIV infection (65), and in OLR lesions it has been isolated in human papilomavirus (HPV) (66), although this causal relation is still disputable. Viral antigens expression is possible in the composition of major tissular tolerance gene. Receptors expression (CD21) for Epstein-Barr virus (EBV) on keratinocytes is more explicit in lichen lesions.

There is evidence of connection between epithelial cell inflammation and herpes simplex (HSV) (23), and disrupted humoral immunity reaction to EBV has also been observed (67).

Autoimmune disorders

The importance of autoimmune reaction in etiopathogenesis is based on studies that observe changes in the T-lymphocyte population in peripheral blood of people with OLR, including a reduced number of CD4+ and CD45RA+ lymphocytes. Such a result, as well as the result of suppressed spontaneous lymphocyte proliferation in peripheral blood mediated by CD4+ and CD45RA+ cells, point to their importance in the onset of this disease (68). Thus, OLR could be linked to many autoimmune diseases and disorders with observed reduction of CD4+ and CD45RA+ cells and possibility causing the onset of autoimmune reactions induced by disordered cellular immunoreactions.

Tissue toleration antigens (HLAs), types: HLA-B8, HLA-DR3, HLA-DR4, present in most autoimmune disorders, have also been observed in people with OLR (69).

According to some authors, OLRE could be classified in concomitant diseases of other autoimmune disorders based on common pathogenesis. Epidemiological investigation of relations between alopecia areata and this disease confirmed that theory (70).

Chronic liver disease

In 1981 Rebora (71) described the possible relation between OLR and specific liver diseases, which was suggested by investigations of many other authors.

Chronic liver disease, as a potential etiologic factor in the onset of OLR, includes chronic hepatitis, especially chronic active hepatitis and primary billiary cirrhosis (72, 73).

According to some authors, clinical manifestation of OLR can very often be linked to particular systemic diseases. Erosive form of OLR can be observed in people with chronic active hepatitis (74).

Such a relation, especially the appearance of the erosive disorder form, was described by Rebora (71). Similar results were reported by other authors who investigated a South European population (75, 76), while research on an Anglo-Saxon population revealed different results (77-79). An epidemiological investigation in Croatia reported liver disease as a potential etiologic factor in the occurrence of OLR (80, 81).

Chronic active hepatitis as a possible etiologic factor cannot be considered a specific marker of this disease, because of the relevant influence of other viruses, such as cytomegalovirus (CMV) and EBV (68). The influence of hepatitis B virus (HBV) has not been entirely investigated, but its role cannot be ruled out from the incidence of this disease (76, 82).

The connection between OLR and chronic active hepatitis, as reported in recent investigations, is aimed at establishing hepatitis C virus (HCV) as the main cause for non-hepatitis A and non-hepatitis B (83, 84). HCV-antibodies have been observed in the serum of patients with OLR, together with a high HCV-RNA prevalence in erosive form of disease (85). The appearance of OLR has been observed in more than 5% of patients infected with HCV, and a great portion of those with OLR, even 60%, with high values of hepatic tests could be HCV seropositive (86).

Formation of antibodies based on liver-kidney microsomal antigen, socalled LKM, or antinuclear antibodies that induce HCV have been observed in some patients with autoimmune chronic hepatitis (86). The result of specific hepatitis antibodies (anti-GOR) is also characteristic for this liver disease (87, 88).

Such guidelines in the study of numerous etiologic factors contribute to an entirely new approach, supporting the autoimmune theory at the onset of that frequent oral disease. Higher values of anti-KLM antibodies in patients with OLR is not obligatory, but in patients with chronic active hepatitis and confirmed OLR diagnosis, and those with OLR without chronic active hepatitis, test results of anti-GOR antibodies in serum are often positive (89, 90).

It is certain that in OLR, as a consequence of classic cell mediated immunoreaction to many foreign antigens, HCV is not the only responsible antigen, since other viral antigens, like HBV, can play an important role in the etiology of this disease (91).

Diabetes mellitus and hypertension

Diabetes mellitus is often described as the essential etiologic factor for the onset of OLR. Disorder in metabolism of glucose is reported in a great number of patients with OLR (92), which is also confirmed in epidemiological investigations on the Croatian population (80). In contrast, some studies found low prevalence of OLR in large groups of people with diabetes mellitus, indicating possible connection with antidiabetic therapy (93, 94).

Investigation of hypertension in the etiologic background of OLR did not reveal significant relation (95). In 1966 Grispan reported 7 patients with OLR, with diabetes mellitus and hypertension. This is known as Grispan syndrome. Recent investigations consider this primarily as described lichenoide reaction caused most probably by therapy for diabetes mellitus and hypertension (96).

Intestinal diseases

Possible etiologic background of ulcerous colitis in the onset of OLR has been described (70, 75, 97, and 98). Other intestinal diseases with potential relation to OLR are celiac disease (97, 99), and Chron's disease, which is becoming more important in the etiology of OLR (100).

Psychogenic factors

Relation between the incidence of LR, with emphasis on OLR, and emotional stress situations can be found in literature (101). Comparison with a control group revealed statistical significant difference in the various psychological profiles of patients (102). Depression tendency has been noted in OLR, and anxiety has been reported as a potential cause of this disease (103, 104). We can assume that chronic discomfort in the mouth of patients with OLR caused by the disease can be understood as stress, creating a closed circle of disease persistence.

The latest research emphasizes the relation between stress and particular immunoreaction. Intensified excretion of hypophyseal hormones, ß-endorphins, with supposed relation to stress, stimulates the growth of lymphocytes, and represents the chemotaxic factor for mononuclears in blood (105).

Neurotic tissue and neuroendocrin cells in different organs excrete endorphins, one of three groups of endogenous opyoids, together with encephalin and dinorphine, which directly participate in immunoreactions and cellular proliferation (106).

Primary and secondary lymphatic organs receive the signals from the nervous system through neuroendocrine mediators and classic neurotransmitters. Conclusive evidence shows the numerous effects of catecholamine, acetylcholine and other different neuropeptide on lymphocytes and macrophages. Noradrenalin and acetylcholine have been released on the nerve endings of sympathetic and parasympathetic postganglionic nerves in peripheral and secondary lymphatic organs. Peptidergic innervation constitutes nervous fibers which release neuropeptid Y (NPY), substance P (SP), vasoactive intestinal peptide (VIP), somatostatin and other neuropeptide. The activity of the lymphocytes affect neuropeptide in the lymphatic tissue, including the lymphatic tissue of oral mucous membrane, through blood circulation from hypophysis and other sources as encephalon, endorphins and the ACTH (adrenocorticotropic hormone), which are increasingly excreted during stress (107).

The mucous membrane in the body, hereby the oral mucous membrane, with a big population of lymphoid cells and rich autonomic innervation, are central points for action of local neuropeptide immunoregulators. Antigen stimulus of mucosa provokes local immunoregulation and excretion of peptide neurotransmitters in a broader innervation area. Extracted neuropeptides change the activity of lymphocytes that have no direct relation to antigen. Neuropeptide VIP, SP and somatostatin induce the function of T-lymphocyte, like impulse for IL-2 extraction. In this way also, the presence of antigens can stimulate local immunoreaction (107).

The best studied neuropeptide immunoregulators, opioid peptide, affect mostly functions of T-lymphocytes and B lymphocytes, NK-cells, monocytes, macrophages and granulocytes (108).

Under the influence of stress, which occurs in people with OLR as a consequence of the disease itself or some other external, psychogenic cause with the simultaneous appearance of genetic predisposition for OLR, it is possible to expect immunoreaction similar to that occurring in OLR (109). It is probable that a specific part of the population is more sensitive to evolution of OLR, thus the disease

in such people can occur with a certain degree of stress that does not have to induce the disease in the rest of the population.

Other etiologic factors

The incidence of OLR has been linked to numerous organism conditions in patients. The appearance of oral lichen is possible in people with other skin diseases like psoriasis and lichen sclerosus (110).

Preliminary findings reveal 6 to 12 times more frequent urolithiasis in people with OLR, but such findings are too scarce to be firmly accepted (111). As a possible etiologic factor the occurrence of glomerulonephritis, the bilious tartar and even Turner's syndrome with associated endochrinopathy can not be disregarded (75, 112, and 113).

With the above etiology, trauma is not reported as a certain cause in the onset of this oral disease, however, it can be supposed that the mechanism of trauma, together with other etiological factors, can contribute to the onset of OLR and intensify the oral symptoms (114).

Pathogenesis of OLR

Numerous reports emphasize the importance of immunological events, with stress on cellular immunity as a key to the pathogenetic mechanisms of the onset of OLR.

The appearance of oral and cutaneus lesions with clinical and histological manifestations like lichen ruber have been observed in people with graph vs. host disease (GVHD) induced by epidermotropic, MHC specific, autoreactive T-lymphocytes (5, 115). The use of immunosuppressive therapy, whose major consequences are suppression of cell mediated immunity, reduction of lymphocyte inflammatory infiltrate and improved clinical manifestation of disease (116, 117), the immunological reaction in the epithelium layer of basal cells, where lymphocytes play a crucial role, is the basic mechanism, although the responsible antigen has stillnot yet been defined (23).

Boisnic (118) proposed two basic hypotheses for the pathogenetic and immunological events in OLR:

- Alteration of keratinocytes, as a consequence of unknown antigen activity, causes the transformation of keratinocytes that stimulate the beginning of an immunological reaction.
- Primary immunological reaction causing the change and degeneration of keratinocytes.

Antigens that could be responsible for the beginning of the immunological reaction are unknown, but preliminary studies report the presence of epidermal antigen specific for lichen planus (LPSA) in granular and deeper areas of spinosal layer in biopsy samples of cutaneus LR (119).

Toto (120) considers the autoimmune reactions as the essential pathogenetic mechanism of all OLR activities. This theory includes the stimulation and proliferation of CD4+ lymphocytes which extract numerous mediators like TNF-ß, that can destroy keratinocytes and IFN-G which stimulates the expression of HLA-II on keratinocytes membrane which excrete other cytokines, and hereby the activation cycles of keratinocytes and immunological reactions become closed.

Mononuclear cellular inflammatory infiltrate primarily consists of CD3 lymphocytes and a smaller number of macrophages, B-cells and mast-cells. The CD3 lymphocytes are of CD45RO+ phenotype, whose activation assure easier recognition of a foreign antigen (121).

The changes in endothelial cells along blood vessels supplying inflammatory area are impulse to recirculation, i.e. amplified accumulation of leukocytes to this area. These changes include the expression of specific adhesion molecules on endothelial cells, which are then specifically connected with appropriate ligand to the surface of circulating leukocytes, causing their adherence to the blood vessel wall and stimulating their migrational ability to the inflammatory area (122).

Intercellular adhesion molecule 1 (ICAM-1) (CD54), as well as the vascular adhesion molecule 1 (VCAM-1) (CD106), are two kinds of the adhesion molecules included in the mechanisms of connecting and transendothelial migration of leukocytes towards the inflammatory area. These molecules have different roles. The molecule VCAM-1 is most probably the mediating adhesion of the T-lymphocyte to activate endothelial cells, while molecule ICAM-1 plays an important role in amplification of their adhesion and transmigration (123).

The molecule ICAM-1 belongs to the immunoglobulin super family of adhesion molecules, its expression is shown in vascular endothel of small blood vessels in healthy tissue. Its ligand is molecule LFA-1 (lymphocyte functional antigen-1) to which it connects, and whose expression is shown in circulating leukocytes and lymphocytes. The relation ICAM-1/LFA-1 is important in adhesion of circulating leukocytes for vascular endothel stimulating migration of leukocyte and lymphocyte to the inflammatory area (124). *In vitro* stimulation of molecule ICAM-1 expression in endothelial cells showed its amplification in the presence of cytokine IL-1, TNF-α and IFN-γ (125).

The molecule VCAM-1 also belongs to the immunoglobulin super family of adhesion molecules and is not visible in vascular endothel of healthy tissue. Its *in vitro* expression is amplified in the presence of IL-1, IL-4 and TNF-α. Its ligand is the molecule VLA-4 (CD29/CD49d), from the group of ß1 integrins (125).

In inflammatory lesions the expression of molecule ICAM-1 is visible on numerous cells including macrophages (122), keratinocytes (120), and in healthy tissues expression is visible on dendritic cells, i.e. Langerhans cells (127). The expression of molecule VCAM-1 is visible in inflammatory lesions, on macrophages and dendritic cells (128).

The above mentioned notion of this important molecular level intercellular immunological interaction suggests potentially important role of adhesion molecules in the pathogenetic mechanism of OLR.

The expression of molecule ICAM-1 on keratinocytes can be seen in inflammatory lesions of OLR in the presence of intraepithelial mononuclear cellular infiltrate, and depends on concentration gradient of cytokine extracted by keratinocytes. In this way, adhesion interaction of molecules ICAM-1/LFA-1 can enable the migration and accumulation of inflammatory cells in the epithelium. The expression of molecule LFA-1 in mononuclear inflammatory infiltrate depends on the expression of molecule ICAM-1 on keratinocytes and lymphocytes (129).

The presence of Langerhans cells and macrophages in inflammatory lesions further stimulates the pathogenetic mechanism for the onset of OLR, presenting the antigen to young, naive and memory T-lymphocytes which are capable of inducing primary and secondary immunological response (129).

The presentation of antigens has a special place in numerous interactions of antigen presenting cells (APC) and T-lymphocyte. The presentation and recognition of antigens is possible through molecule MHC on APC cell membrane and through T-lymphocyte receptors (TCR). The connection between the molecule ICAM-1 expressed on the APC cell and the molecule LFA-1 expressed on T-lymphocyte is important in activating T-lymphocytes. Other molecular interactions between T-lymphocyte and APC cells, as interaction VLA-4/VCAM-1, are important to antigen presentation of T-lymphocytes. Dendritic intraepithelial cells that express the molecules CD1a, CD14 and VCAM-1 confirm possible expression of molecule VCAM-1 on Langerhans cells, which points to its activation and possible interaction with molecule VLA-4 expressed on memory T-lymphocytes (121).

The expression of molecules ICAM-1 and VCAM--1 in the thick inflammatory infiltrate corresponds to the presence of CD14+ macrophage. In deeper layers of inflammatory infiltrate, the macrophages that on its surface express molecule CD14 have similar distribution as dendritic cells with the expression of molecule ICAM-1. The molecule VCAM-1 is a marker for macrophage activation, directly connected to memory T-lymphocytes through molecule VLA-4. This interaction is closely related to the pathogenetic mechanism of OLR (121).

It can be said that, in OLR, Langerhan cells are activated and of major factors in the pathogenetic mechanism of this disease. They express MHC antigen, class II, HLA-DR, and in OLR is observed higher expression of HLA-DP and HLA-DQ indicating their activation. Antigen presentation by Langerhans cells to T-lymphocytes which then recognize it give impulse to excretion of cytokines which then recirculate and activate other T-lymphocytes and macrophages. The results of macrophages in inflammatory infiltrate which express the molecule CD14 on their surface, as well as the expression of molecules ICAM-1 and VCAM-1, points to their important role in the pathogenetic mechanism for the onset of OLR (121).

It can be assumed that the pathogenetic process for onset of this disease is most probably motivated

by the presence of an unknown antigen in the epithelium of oral mucous membrane. The antigen is presented to CD4 lymphocytes through Langerhans cells which are then activated and cause accumulation of CD8 lymphocytes which can cause a defect of keratinocytes. Activated CD4 lymphocytes extract IFN-γ which induces stronger expression of HLA-DR antigen on keratinocytes, enabling permanent persistence of antigen presentation to T--lymphocytes (131).

The characteristic findings in lesions of OLR are a consequence of the above mentioned sequence of events with consequences in the form of vacuolar degeneration, basal epithelial cells lysis and, finally, liquefaction degeneration of the basal cellular layer with ribbon-like infiltration of lymphocytes in lamina propria.

Conclusion

OLR is a mucocutane autoimmune disease with still unexplained etiology. The pathogenetic mechanism stimulated by multifactor activity of numerous factors is based on cell mediated immunity, with autoimmune reaction as a key to all events in OLR. Such an approach to the etiology and course of the disease gives appropriate guidelines for diagnostics and therapy, and thus for understanding OLR. This includes tissue standardization in assertion of the antigen for tissue tolerance in families where a number of members had this disease, detection and treatment of other systematic autoimmune diseases, detection and treatment of systemic metabolic diseases with increased attention to diabetes mellitus and chronic liver disease, in which oral lichen can be observed, without ignoring systemic therapy used for that, and removal of all local and systematic provoking factors.

Revealing the true cause of the onset of OLR will enable adequate targeted therapy, which could lessen the duration of unpleasant oral symptoms, reduce recurrence of the disease, prolong the remission stages with the potential of a complete cure.

Since OLR is a precancerous lesion, special attention should be paid to detecting and monitoring patients, regardless of the clinical lichen form. It is assumed that atrophic, erosive and ulcerous lesions have more frequent malignant alterations, and because of the possible transfer from one form to another, particularly during recurrence of the disease, other forms, such as papular and reticular, also need the appropriate approach to diagnostics, therapy and control of patients.

It is important to include the diagnostic trio: thorough case history, clinical and histopathological diagnosis. Lichen ruber is a disease with a chronic character that requests continued control of the patient, and obligatory rebiopsy of the lesion every 5 to 12 months.