Oral Lichen Ruber - II Immunoreaction

Dolores Biočina-Lukenda

Zavod za oralnu medicinu
Stomatološkog fakulteta
Sveučilišta u Zagrebu

Summary

Immunological disorder in oral lichen ruber (OLR) is related to cell mediated immunological reaction which can imply various immunological disorders in the oral mucous membrane. Changed immunoreaction characterized by suppressed function of phagocyte and NK-cells reduce the possibility of elimination of the bacterial antigens with possible resultant onset of autoimmune disorders, stressing the importance of nonspecific immunity. Evaluation of cell mediated immunity is based on phenotypic and functional analysis of peripheral blood cells by monoclonal antibodies. T-cell mediated suppression has an important role in maintaining its own tolerance, so the disorder of T-cells is included in the pathogenesis of autoimmune diseases. A consequence of this could be activation of immature T-lymphocytes, causing cellular autoreactivity in OLR. Disorder of cell mediated immunity could reflect on the humoral immunity condition. Humoral immunity in patients with OLR has been reported, but with inconsistent results. The result of humoral immunity is not specific, but is a consequence of the changed immunoreaction of patients with OLR caused by other immunological disorders and diseases where oral lichen could manifest

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Address for correspondence:

Mr. sc. dr. Dolores Biočina-
-Lukenda
Zavod za oralnu medicinu
Stomatološki fakultet
Gundulićeva 5, 10000 Zagreb
Croatia

Introduction

Our environment is full of various pathogens, e.g. bacteria, viruses, fungi, protozoa, or multicellular organisms. Every one of these pathogens may provoke the disease, permanent damage, or even death of an organism. The immunological system and the multiplicity of immunological reactions determined by the entrance point and type of the pathogen-antigen have a crucial role in prevention of such undesirable effects on the organism.

Thus, the organism must resist numerous foreign agents to survive whether in the form of individuality loss by merging with some other organism, entry of harmful substances, microorganisms, parasites or danger from its own cells that changed behaviour and location in tissue. Immunity of all defensive mechanisms is included here in its widest sense for the purpose of defense, even those most primitive without specificity or memory. Such immunity is characteristic of only living creatures, developing together during evolution, with defense from infection, defense from tumors, and maintenance of antigenic and genetic homeostasis, considered the most important functions of the immunological system.

Although the immunological system functions to protect the organism from harmful environmental influence, there are circumstances under which the effects of the immunological system can damage the host organism causing the occurrence of autoimmune diseases. The reason for this is inefficiency of the immunological reaction, too powerful immunological reaction or the creation of antibodies for its own cells, i.e. specific cellular structures. Antibodies can be directed against epithelial cells, including oral epithelial cells, causing the appearance of mucocutane autoimmune diseases, including lichen ruber planus.

Immunoreaction in OLR

As mentioned above, oral lichen ruber (OLR) is an autoimmune disorder in which systematic metabolic disorders as possible etiologic factors can reflect on the systematic and local immunoreaction of patients.

Connection between immunological disorder in OLR and cell mediated reaction is assumed, which could implicate different immunological disorders in oral mucous membrane (1, 2).

According to Morhen's hypothesis (1), OLR is a disease without known etiology or caused by the activity of specific external and internal, unknown antigens. The total number of Langerhans cells (LC) in the epithelium is increased, and CD4+ cells are a major part in cellular epithelial infiltrate. In addition, keratinocytes in the basal layer of the epithelium, in OLR lesions, express on their surface the antigen HLA-DR. This result reveals their activation of IFN-γ, excreted by CD4+ lymphocytes. The infiltrate of CD8+ lymphocyte is placed immediately below the epithelium, and causes destruction of the basal layer of keratinocytes. Co-stimulating signals, as a result of outer, foreign or maybe some inner antigens, induce the adequate immunological reaction of T-lymphocytes to that antigen. Changed reaction of T-lymphocyte to keratinocytes in the basal epithelium layer could be explained by molecular mimicry, when activated T-lymphocytes react to a foreign antigen, although, in fact, the mutual similarity between the foreign and its own antigen could cause further autoimmunization.

Boisonic (3) proposed two basic hypotheses on immunological and pathogenetic events in OLR, where the above mentioned alteration and degeneration of keratinocytes stimulates the beginning of the immunological reaction or the immunological reaction alone causes transformation of keratinocytes.

Unspecific immunoreaction in OLR

Changed immunoreaction lessens the possibility of eliminating the antigens for bacteria, stressing the importance of nonspecific, innate immunity as the first defensive barrier.

Changed immunoreaction caused among other things by functional disorder of NK cells could result in the appearance of autoimmune disorders, including OLR, because antigens, probably bacterial, can freely expand in tissues of oral mucous membrane (4-6).

The total number of NK cells in peripheral blood of patients with OLR is decreased, with preserved function of suppressor cells. Since IL-2 and IFN-γ can intensify the activity of NK cells, decreased values of NK cells relate to possible indirect connection with cell mediated reaction where suppressor/inductor subpopulations of lymphocytes CD4+ that excrete IL-2 and IFN-γ have an important role. It is assumed that suppressed activity of NK cells is related to disorder in PMN leukocyte system in OLR, making an additional factor in the pathogenesis of this disease (7). The result of reduced NK cell portion in the peripheral blood of patients has been described by Biočina-Lukenda et al. (8). In contrast, some results do not reveal changed function of NK cells, but only slightly lowered values of total NK cells and PMN number in the peripheral blood of patients with OLR (5).

Simon et al (7) point to the mechanisms of NK cell functions that could be related to chronic disease such as OLR. Numerous signals, as co-stimulators, can affect the function of these cells. Thus, even NK cells can have autoimmunoregulatory function, excreting proper cytokine, such as IFN-γ, IL-2, IL-12, that have an activating effect on NK cell. Besides this, it is important to emphasize that spontaneous cytotoxic activity of NK cells depends on their continuous exposure to IL-2 effects.

Suppressed action of prostaglandin (PGE1, PGE2, PGA1, and PGA2) on autoregulation and interferon regulation of NK cells function has been described (7). Such data could be related to weakened function of NK cells, since it is known that prostaglandins have been released in inflammatory tissues, including the mucous membrane tissue affected by OLR.

It could be said that the effects of IFN-γ and IL--2 are potential activators of NK cell functions, while prostaglandins and suppressor/cytotoxic CD8 lymphocyte are responsible for inhibition of the NK cell function in OLR (4).

The evaluation of phagocytic cell functional ability shows greatest changes. Suppressed function of the phagocyte was reported stressing spontaneous mobility and ingestion (6). Spontaneous mobility and ingestion are especially suppressed, and digestion values increased at the beginning of the disease. Other authors (9) who observed changed function of phagocytes, where spontaneous mobility, ingestion, digestion and cellular cytotoxicity that depend on antibodies-ADCC were significantly decreased, report similar results.

Such a result of phagocyte function indicates a serious disorder that must be emphasized in understanding the mechanism of OLR genesis. It could be assumed that this disorder can play an important role in the pathogenetic mechanism of OLR, because of reduced antigen ability to eliminate bacterial antigens in that way. Other authors have reported similar results, describing a reduced number of PMN in the peripheral blood of patients with OLR, thus the disorder of PMC leukocyte system could be considered an additional factor in the pathogenesis of this disease (5, 9, 10).

Such a description of nonspecific immunity indicates that reduced share of NK cells in peripheral blood and their suppressed function, could cause changes in immunoreaction, and be included in the pathogenetic mechanism of this disease as a possible consequence of the disorder in developing adequate reaction of innate immunity to outer antigens.

Cellular immunoreaction in OLR

The evaluation of cell mediated immunoreaction is based on phenotypic and functional analysis of peripheral blood cells by monoclonal antibodies. Recent findings report that the share of T-lymphocyte in the peripheral blood of patients with OLR can be increased, i.e. the cellular immunoreaction is activated. Investigations of CD4+ and CD8+ T-lymphocyte subpopulations share, report increased share of CD4+ T-lymphocyte and decreased share of CD8+ lymphocyte. Increased number of CD4+ T-lymphocyte causes a greater rate of cytokines excretion which then activate the CD8+ lymphocytes able for lysis of cells. Such findings confirm systemic immunological reactivity in OLR. The lymphocytes in peripheral blood show normal values (11). In contrast, results of an increased number of T-lymphocyte and unchanged share of B lymphocyte in the peripheral blood of patients have been reported, and the share of lymphocyte subpopulations has not changed significantly (12).

Many investigations have showed that T-cell mediated suppression has an important role in the maintenance of its own tolerance, thus the disorder of suppressor cells is included in the pathogenesis of autoimmune diseases. Suppressor T-cells monitor the course and specificity of cell mediated immunoreaction, determined by T-cell reaction. This reaction includes T-helper cellular activity, supersensitivity, cytolitic activity of T-cells and proliferation of T-cells. Damage to T-cell mediated suppression could lead to activation of young, immature T--lymphocytes which differ from mature memory cells. Such loss of suppression function could cause cellular autoreactivity in OLR (13).

By monoclonal antibodies anti-CD45RA and anti-CD29 two functional CD4+ T-lymphocytes subpopulations with suppressor/inductor, i.e. helper/ /inductor activity have been defined (14).

Through cellular markers in patients with OLR young, immature and memory cells inside CD4+ and CD8+ lymphocytes have been identified pointing to a different stage in the clinical evolution of disease. Course of the disease probably corresponds with the activation of CD4+CD45RA+ cells which further differentiate in CD4+CD45RA- cells. Functional and phenotypic conversion of suppressor/ /inductors CD4+CD45RA+CD29- T-cells in helper/ /inductor CD4+CD45RA-CD29+ memory cells have been suggested. Such stimulation of lymphocytes effects the phenotypic transformation which could lead to autoreactivity in OLR (14, 15).

The functional analysis of lymphocytes from the peripheral blood of patients with OLR is expected to show spontaneous lymphocyte proliferation. This result should be more expressed in the later course as well as in the erosive form of the disease (16). It is assumed that such a reduction of spontaneous lymphocyte proliferation could effect activation of lymphocytes from peripheral blood (17).

By amplification of T-lymphocyte activity, stimulated by herbal mitogenic PHA (phytohemaglutinin), it is possible to detect a disorder of cellular immunological reaction in patients with OLR. Amplified stimulation of T-lymphocyte activity with PHA has also been observed in other studies (14, 17).

Spontaneous proliferation of the lymphocyte may be especially reduced in the course of the reduction of young, immature CD4+ (CD4+CD45 RA+) lymphocytes and enlargement of CD4+CD 45+RO+ and CD29+ memory cell share (18).

Stimulation of the lymphocyte proliferation by mitogenics can be changed in OLR, but not in all cases. Mitogenic stimulated lymphocytes do not excrete cytokines adequately, like TNF-α, IFN-γ, IL-2, IL--6, because of its suppressed function (19). M-RNA was isolated in cultures of T-lymphocytes from OLR lesions for IL-2, IL-4, IL-10, TNF-α and TGF-ß1 by PCR method (polymerase chain reaction) (20).

Reduced cytokine production by lymphocyte can be regulated by stimulation with PHA (fitohemaglutininom), PMA (phorbol myristat acetate), as any disorder in cytokines production is primarily related to reduced activity of T-lymphocyte, and not to reduction of CD4+ T-lymphocyte or enlarging of CD8+ lymphocyte share that have been found in people with OLR (19, 21). The result of different lymphocyte subpopulations, CD3+, CD4+, CD8+, CD8CD45+, and changed proportion of CD4/CD8 and CD8CD45RO+/CD8CD45RA+ cells points to changed T-cells mediated immunoreaction (22).

Increase in T-cell suppressor activity within lymphocyte infiltrate in OLR lesion can cause misbalance between helper T-lymphocyte activity and suppressor T-lymphocyte, providing the base for immunoactivity in lymphocyte infiltrate of the epithelium. Different *in vitro* investigations reveal that T-cell activity does not have to reflect the whole spectrum of immunoregulation between lymphocyte subpopulations in inflammatory infiltrate (13).

The T-lymphocyte in lesions of OLR have intensified excretion of GM-CSF (colony stimulating factor, granulocyte-macrophage colony), IFN-γ, TNF-α, IL-6, IL-2, revealing that local cytokine production is tied in continuous sequence of immunological events (19). It was also noticed that keratinocytes excrete GM-CSF, IL-6, IFN-γ, TNF-α, influencing directly activation of T-lymphocytes in the infiltrate and proliferation of lymphocytes B (23).

In OLR lesions the result of CD1a+, CD80+, CD86+ and CD25+ cells have been observed that morphologically correspond to Langerhans cells (24). Total number of Langerhans cells (LC) in OLR lesions has been unchanged or increased. These cells can on their surface express HLA-DP, HLA--DQ or HLA-DR antigens, caused by local cytokine production (25). In that way, antigen presentation by T-lymphocytes is enabled after which their interaction is established by joining lymphocytes through the molecule that represents ligand to adhesion molecule expressed on the antigen presenting cell. Since, beside the epithelium cells of vascular tissues, macrophages and dendritic cells as mentioned earlier, keratinocytes of epithelium can on their surface express adhesion molecules, their interactions with T-lymphocytes is enabled initiating their accumulation in the inflammatory infiltrate of epithelium and further course of immunoreaction (26-29). Immunohistochemical research has revealed the role of MAST cells whose degranulation causes the release of TNF-α, regulating the excretion of cytokines and the function of T-cells. This course of events could be the possible cause of chronic evolution of the disease (30).

The latest studies report that collagen of extracellular matrix, type IV and type VII, is more expressed in BM area in OLR and ß1 integrins could be present on the lymphocyte surface in inflammatory infiltrate. The expression of adhesion molecules on inflammatory infiltrate and antigen MHC--II cells have been intensified, as mentioned before, by local cytokine production (13).

Humoral immunoreaction in OLR

Cell mediated immunoreaction disorder can effect the condition of humoral immunity (31).

A few authors have described changed humoral immunity in patients with OLR. However, reported results were different.

Some authors (32) in their study describe a reduced level of serum IgA and IgM, while others (33) observe only reduced IgA values in serum. Investigating the level of serum imunoglobulin, Griffith (34) did not find difference in a group of patients with OLR, compared to a control group of healthy people. Obtained results show that the level of IgG in serum increased in 23% of the examined patients with OLR. In 44% patients with clinical manifestation of erosive form of OLR, levels of IgG and IgA in serum are increased. Schröder (35) also observed extremely high values of IgG in patients with erosive form of the disease, as well as in patients with synchronous appearance of oral and skin changes. In contrast to the aforementioned, there are results which have not revealed changed values of immunoglobulin level in serum with oral and skin changes of lichen ruber (LR) (36), while Sklavounou (37) found increased values of IgG and decreased values of IgA, with unchanged level of C3 and normal level of C4 component of complement in serum. In his research, Nigram (38) described decreased values of the level of IgA and IgM. In his study, Lundström (31) reports increased values of IgG level, and obtained values of IgA and IgM did not show exception in people with OLR. Other authors (39) report increased values of serum IgA and IgM level, while values of serum IgG remain unchanged.

The result of increased values of IgA in serum, as the main protection for all mucous membranes in the organism, could be an indicator of induced immunological reaction in this disease. Immunoglobulin IgA is the main immunoglobulin in extravascular liquids, whose basic task is local protection of mucosal surfaces. Given the fact that OLR is a disease of oral mucous membrane, increased values of IgA in the serum of patients give insight into adequate humoral immunoreaction to foreign antigen (39). However, decreased (32, 33, 37, 38) or unchanged values of immunoglobulin IgA in serum of patients (31, 34), are mostly reported as a possible consequence of changed immunoreaction caused by other immunological disorders within which OLR could manifest.

Increased values of serum IgM contribute to the apprehension of OLR, and point to acute inflammation where the appropriate immunoreaction to specific bacterial antigen has been induced, since this immunoglobulin is created in primary immunoreaction, and its most important role is protection of intravascular space from bacteremia (39). The results of unchanged or even decreased values of serum IgM in people with OLR point to changed humoral immunoreaction because possible immunodeficiency with hypogammaglobulinemia is reported in the composition of which that disease can reveal (31, 34). Variability of literary data is probably linked to sampling in different evolutionary stages of the disease.

Some authors observed deposits of IgM in basal membrane area in lesions (BM) together with findings of fibrin and fibrinogena (40, 41, and 42). Mora (41) describes deposits of C3, C4 and C5 component of complement in BM area. IgM, C3 and C4 in colloid bodies have been observed (40), with occasional clusters of IgG, IgA, C1 and C5 (41, 42). These results are a consequence of intensive immunological action in the lesion, where amplified cytokine production of T-lymphocytes has induced proliferation of lymphocyte B.

The components of complement C3 and C4, are part of a complex biological system, whose induced cascade activation through creation of final complex aims at cell lysis. By investigating C3 and C4 components in the serum of patients with OLR, the aim is to define the efficiency of this mechanism by the function of eliminating possible bacterial antigens in OLR.

Reports on the complement function in patients with OLR are very rare. Reports in literature are mainly based on tissue investigation results. There are no data on changed values of C3 and C4 components of complement in the serum of patients (37). However, C3 and C4 deficit in serum could cause diseases such as pyogen infections by *Staphylococcus*, *Streptococcus* or even *Naisseria* (43). C3 deficit is behind SLE (Lupus erythematodes systemicus), mixed essencal kriogammaglobulinemia and diseases caused by immunocomplexes as glomerular nephritis, within whom OLR can be observed (44).

The result of humoral immunity reaction is not specific, but it is a consequence of changed immunoreaction in patients. A reason could be other immunological disorders in the composition of which the lichen ruber could manifest, like rheumatoid arthritis (RA), the Sjögren syndrome, autoimmune hepatitis, sarcoidosis, scleroderma, vitiligo (RA). Possible immunodeficiency with hypogammaglobulinemia has been suggested as a reason for changed humoral immunity in OLR, with described occurrence of generalized lichen ruber in HIV disease (46, 47).

The insight of the complete literature reveals differences in immunoreactivity connection in patients with OLR with regard to possible etiology and pathogenesis of this disease.

Conclusion

Stimulated by the activity of a still unknown antigen, immunological reaction in OLR has changed. Thus the autoimmune background of the disease based on cell mediated immunity has been confirmed. Such immunity disorder in patients with OLR is particularly characteristic at nonspecific immunity level, disabling adequate elimination of foreign antigens. Inadequate nonspecific immunoreaction can also be reflected on other immunity forms.

The role of the subepithelial lymphocyte infiltrate is mediated by cytokine activity whose excretion is stimulated by adhesion molecule expression and connection to specific ligands. Consequently, established cooperation between antigen presenting cells, limited lymphocyte and epithelial cells results in damage to keratinocytes and basal membrane. This damage is primarly caused by cytotoxic CD8+ T-lymphocytes T. Increased number of CD8+ lymphocytes indicates the autoimmune genesis of OLR. T-lymphocyte activation and resultant excretion of specific cytokine activation cause a closed circle of cell mediated immunity. Immunoreaction in OLR can be manifested as hypersensitive reaction, type IV, as a response to causal antigen, in which case keratinocytes with a changed structure, thus changed function.

Humoral immunoreaction in OLR is changed, nonspecific with different results in various authors. The result of changed humoral immunoreaction in people with OLR points to activation of specific systematic disease behind OLR, where OLR can manifest.

The aim of this paper is to give an insight into complete immunoreaction in OLR. Although this paper is not the final key for understanding the oral lichen, it describes the immunoreaction as pathogenetic mechanism in the genesis of this disease.