ORAL LICHEN PLANUS – RELATED CONNECTION WITH HLA-SYSTEM ANTIGENS

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ABSTRACT

Aim: To determine whether there is an immunogenic connection and antigen difference between the HLA antigens in the erosive (EOLP) and reticular (ROLP) oral lichen planus.

Materials and Method: 73 patients with ROLP and EOLP have been tested. Typing of the HLA antigens has been made for locus A and B. The typing of the HLA was conducted with the use of microlymphocytotoxic test by Terasaki. The reading of the findings has been conducted with an inverse microscope. When a reaction has 4 points it is considered to be positive.

Results: The most frequently typified antigens in ROLP from locus A are HLA A2 (57.57%) and A3 (33.33%), and for locus B 21.21%. In EOLP it is A9 (88.88%). In locus B a connection has been found with HLA B8 (77.77%). The statistical analysis with the χ^2 test has shown that the carriers of HLA A9 display a relative risk (RR) of 3.65 and $\chi^2=20.72$. Consequently, there is high static importance for locus A $p<0,001$. For locus B, In EOLP for HLA B8, $RR=6.7$ $\chi^2=37.64$ and $p<0,001$. ROLP has shown association with HLA A3, where $RR=2.31$ and $\chi^2=9.14$ and $p<0.05$.

Conclusions: In ROLP A3 antigen and in EOLP A9 and A8 may be considered as carriers with proneness to OLP.

Keywords: oral lichen planus, erosive, reticular, HLA, squamous-cell carcinoma

INTRODUCTION

Lichen planus (LP) often is a mucocutaneous chronic inflammatory condition, which basic and main efflorescence is the present pathognomic papule. In the clinical development an erosive-ulcerative transformation or a vesiculo-bullous manifestation is possible. [1]

In the literature they are acknowledged and in the clinical practice several clinical forms of the

lichen planus (OLP) have been confirmed to exist: reticular, plaque, atrophic, vesiculobullous and erosive form. In most cases the erosive form epithelializes, but in 1% of the cases it is possible that it will transform in a squamous-cell carcinoma. Consequently, there are many reports for the malignant potential of OLP. [1]

LP can be localized just on the oral mucosa (15-20%) or, at the same time the oral lesions can be monitored with cutaneous changes (60-70%). [1] The same, in certain number of cases, can be scattered exclusively on the surface of the skin, which will manifest itself in 1-2% of the population.

The disease is dominant in the age groups ranging from 30 to 60 years, as it is the fact that the disease is rare among children and adolescents and almost never manifests itself on people that are in the senile period. The authors are in accordance with the fact that the frequency of the disease is more common among the female population, rather than the male population. [2]

However, based on the several polyaspect researches of OLP, the modern medicine with certainty emphasizes the fact that this disease is relatively common among the population. This is confirmed by data and information from many authors. [3, 4]

The most common localization of OLP is in the cheek mucous membrane, in retromolar trigone as well as in the length of the masticatory line. Sometimes the papule can also include the side edges of the tongue, or the specific and characteristic mucous patterns that are present in the apex, as well as the dorsal area of the tongue. Extremely rare, almost never, OLP is not found on the hard palate and the gingiva [5] besides the somewhat shaped stands in terms of the predominance in the prevalence of the lesions in OLP, however, still there isn't a unified stand in terms of this condition. Through their own studies certain authors came to the awareness that the common place of occurrence for OLP beside the retro molar trigone of the buccal mucous membrane is the apex of the tongue. [6], Figure 1 and figure 2: Reticular form of the oral lichen planus on the oral mucosa.

Figure 1 & 2. Reticular form of the oral lichen planus on the oral mucosa

In contrast with the LP, the lichenoid dermatitis represents a group of inflammatory conditions of the skin with a characteristic clinical finding that can be similar or in other cases different. One group manifests itself with pruritic polygonal, purple flat papule and plaques, and the other lichenoid changes that can be a consequence of the administration of medicines and/or other causes that can influence to change the clinical image. Epidemiologic studies confirm that the classic lichen planus is considered as a disease in adults, the lichenoid reactions can manifest themselves more often among the young population. Sometimes they can be associated with certain disorders outside the mouth such as alopecia. [7, 8]

Without exception, in all forms, one of the major symptoms is cancerophobia with insufficiently clarified etiopathogenic mechanisms, as well as the incredible resistance to therapy, which in its own way suggests the need for conversion of different and, as much as possible, subtle research.

The erosive OLP is the most widespread subtype, which is characterized with serious therapeutic difficulties that often require systematic immunomodulatory therapy, such as oral steroids and immunosuppressants. For several years now the positive therapeutic effects are achieved with the use of extracorporeal photochemotherapy. [9, 10],

Figure 3. Bullous form of the lichen planus

Figure 4. Labial mucosa and lips

Etiopathogenic problems with OLP

Despite the fact that modern science and medicine have at their disposal clinical, histological, histochemical and other methods of research in which electronic and light microscopy is used, immunofluorescent and other trials, the aetiology of OLP is still unknown.

The genetic factors (HLA-DR2), immunologic causes (mediated by T-cells) and the influence of infectious agents (connection with the viral hepatitis C, differences in the oral microflora in OLP) are considered as main predisposing and inductive factors. The management of OLP depends on the seriousness of the lesions. The use of systemic and local corticosteroids which are the primary therapy method, and the oral glucocorticoids are used for severe erosive lesions. [1]

With the expansion of immunology as a recent branch in medicine and in dentistry for a large number of expert associates the unclear etiopathogenesis of this disease was quite a challenge, who then, using the meagre previous knowledge on this subject, continued with further in depth trails and research.

In literature many cases of the occurrence of LP within a family are described, so some authors single out the hereditary predisposition as a leading factor. [11] The exact mechanism of the hereditary genesis has not been proven with certainty, but it is considered that answers lay in the basic hereditary particles and components of the organism that are at the same time the main constitutional markings of a person, and that of course are the genes, which are the main and basic determinants in the creation of the predisposition towards certain diseases. In that context these findings represented a challenge for tracking the correlation between the HLA-antigens and the lichen planus. The obtained results of Lowe [12] prove the presence of the A3-antigen of the HLA system, what in a way is in accordance with our preliminary studies. [13] While Simon [14] in his study proved that there is an immunogenic association with the B8 antigen. Regezi [15] using the immunohistochemical method, concluded that the highest presence of antigens is in the locus.

From all of this, as well as the numerous findings from the literature regarding the possible predisposition of the organism towards LP and its association with the antigens from the HLA-system, it can be deduced that the opinions are mismatched and in a lot of ways contradictory, on account of which the authors still do not have a definitely formed position in regard with this problem. [16, 17]

HLA-antigens and lichen planus

At the beginning the HLA system was considered as a plain leukocyte formula, however later on it was proven that this system shows high polymorphism and that it can be used as a designator of the individuality. With further research of the processes of acceptance and rejection of the transplants, it became clear that this mechanism is controlled by a single chromosomal region in which the genes that function synergistically and play an essential role in the immunological process are located.

There are numerous hypotheses for the explanation of the connection between the diseases. From the fact that the HLA-antigens represent just an index of the genes that regulate the immune response, through the role of the virus receptors, to the theory of molecular mimicry according to which the HLA-antigens are combined with a certain disease through structural and immunological similarities with the cause.

In some studies, the immunological, pathological and clinical relations between the HLA antigens and the oral immunological diseases are described. It is believed that the determining of HLA is useful for early diagnostics, because it allows to anticipate the individuals that are at risk. [18]

In the 80's there was a more intensive search for the connection between human antigens and certain diseases. [19] An HLA typing was made in patients with aphthous stomatitis. The HLAA1 and HLAB2 types were distinguished. The HLA antigen in patients with lichen running in their family was determined. From antigens that are associated to patients with family connections high frequency B7 antigen was detected. [20]

While researching the second class antigens it was deduced that the antigens from locus DR are often present in patients with skin manifestation of lichen planus. [21]

However, there are contradictory findings that deny the aforementioned confirmed results. In the erosive OLP group, the HLA-Te22 antigen manifests itself more frequently among patients with positive ANA (75%, $p < 0,05$), rather than those with a negative ANA (25%). [22] It has been established that there is connection of the HLA-Te22 antigen with ANA among Chinese patients with erosive OLP. [23]

An attempt was made to determine whether there is an immunogenic connection and whether a difference in the antigens will be registered between the HLA antigens in the erosive and reticular OLP. [24]

The literature and the clinical practice confirm that there are differences in the clinical manifestation and the prognosis of the disease among the two most common clinical forms of OLP. As opposed to the reticular, the erosive OLP has an irregular form, eroded and sketchy surfaces, multifocal and sick regions. The reticular OLP is spread on the intact surface with white hyperkeratotic plaques and an incongruous sensation. Likewise, in contrast to the reticular, the erosive OLP has increased potential for development of oral-squamous carcinoma (OSCCs). The possible malignant transformation is between 0% and 5.3%. [25]

According to the World Health Organization, OLP belongs to a category of premalignant regions, hence the advice of the doctors for regular check-ups, a serious approach to the treatment of the disease and avoiding risky and additional factors, such as the use of alcohol and cigarettes which would additionally increase the risk factor for OSCCs. [26]

However, the pathogenesis of the transformation of OLP into OSCCs is still unclarified. Many links in the chain that is malignancy are still unavailable and unknown. The questions that remained unanswered are to which degree OLP is independent from the OSCCs and whether the carcinoma has developed from the OLP or is it just a coincidence. [27]

The malignant transformation was described for the first time in the distant 1965. [28]

The epidemiological data suggests that the malignant transformation of OLP is not equally represented in all the regions of the oral cavity. The erosive lesions which are present on the tongue and the buccal mucosa tend to malignant progression more often. [29] There are facts saying that the malignant transformation of OLP in a patients under the age of 40 is very rare, although there have been cases when OLP showed malignant characteristics in young individuals, even as young as 17 years. [30]

The most common malignant transformation of OLP is OSCCs, with extremely uncertain prognosis and life threatening condition. [27]

The pathogenesis of OLP is very complex and includes a possible antigen presentation from the oral keratinocytes the origin of which can be exogenous or endogenous. [31-33] This antigen activator is accompanied by a mixed inflammatory response that is consisted mainly of T-cells, macrophage, mast cells as well as cytotoxins and cytotoxic molecules. [34]

In short, the current hypothesis says that the chronic stimulation of the inflamed and stromal cells produce signals that cause the epithelial cells

to disturb the growth control and together with the oxidative stress, from oxidative and nitrate products, cause damage of the DNA which results in neoplastic changes. [35]

It is considered that p53 has a pretty important role in the pathogenesis of the malignant transformation of OLP into OSCC. The values of p53 in OLP are increased in comparison with the findings of this molecule in healthy tissue. In essence p53 has been identified as a response of the destruction of DNA [36], and the identification of p53 in OLP is interpreted as an indicator of precancerous potential. [37, 38]

The theory of loss of the heterozygosity (LOH) in the locus 3p, 9p and 17p, which is often noticed in oral carcinomas, were not found in OLP. Even though this result is not typical for OLP as a risky lesion for the malignant transformation, the authors could not exclude the possibility that OLP can be sustainable to malignant transformations through other genetic pathways. [39]

Also, as possible triggers of the malignant transformation the matrix metalloproteinases are mentioned. Some authors informed us about the increased expression of MMP1-3 in the epithelial OLP cells and MMP-9 in the OLL inflammatory infiltrating cells. The authors that support this theory have confirmed a certain influence of the MMPs in the disturbance of the basal membrane, which may possibly enable the intraepithelial inflammatory cellular migration. [40]

The malignant transformation of OLP and OSCC incited an interest among many researchers who directed their research to a molecular level [41, 42], and some others tried to connect them with certain systematic diseases (hepatitis C, colon diseases), seeking out their common attributes. [43, 44]

So far, all findings have shown that OLP is a preneoplastic inflammatory model. The fact that the lesions of OLP are located in an easily accessible environment such as the oral cavity, make this disease available for implementing certain diagnostic procedures (puncture, biopsy) and monitoring of the disease during its evolution. Still, the task that remains for the future is to find the markers which will be used to differentiate the risky patients that are likely to progress to OSCC, from those who would have peaceful controlled episodes and monitoring of the OLP which has no chance to malignant transformation, which is not rare in our everyday practice. Starting from these facts, we aimed to detect the possible immunogenetic connection with antigens from the HLA - system into locus A and B in patients with reticular and erosive form of the OLP.

MATERIALS AND METHODS

A total of 41 patients with clinically diagnosed lichen planus with oral manifestation, based on anamnestic data, subjective and objective findings, were examined at the University Dental Clinical Centre, Department of Periodontology and Oral Pathology, at the Faculty of Dentistry in Skopje.

Lichen changes were localized to the mucous membrane in the retromolar region. All patients with oral lichen planus, in relation to the clinical form, were divided into two groups: with reticular 33 subjects and with erosive 8.

In all subjects, regardless of the form, HLA-antigens from loci A and B were determined.

To compare the results of HLA typing the standards of the National Institute for Transfusiology were used. This group consisted of 1,300 healthy patients who did not have any systemic disease, including lichen planus. Patients with cutaneous manifestation of lichen planus were excluded from this group.

For HLA-antigen typing, the microlymphocytotoxic test according to Terasaki was used.

Method of performance

Patients from the investigated group and both subgroups (reticular and erosive) and the control group were compared to each other according to the HLA-antigen typing in locus A and B.

In patients with lichen planus and the control group in which HLA-antigenic typing was performed, the statistical analysis included determining the antigen frequency (the representation of a particular antigen expressed in percent %) and determining a relative risk factor (RR) for possible associated antigens according to mathematical calculations.

The Microlymphocytosis test according to Terasaki is based on the principle of cytotoxicity, and requires lymphocytes from the persons included in the typing, serum test and the complement, performed at two intervals. First, they are contacted with the examined lymphocytes in test serum, and then complement is added. If the lymphocytes have the appropriate antigens for antibodies from the test serum in the presence of the complement, there will be lymphocytotoxicity. The reaction takes place on microplates i.e. Terasaki plates with liquid paraffin.

The lymphocyte mass is obtained from 10 ml. Periphery heparinized blood (10 units heparin per

1 ml / blood). An equal volume of blood is mixed with a physiological solution and placed carefully on a 10 ml gradient ficoll triosyl of specific gravity 1076. Separation of lymphocytes and other actions takes place in plastic or glass silicone packing. Then follows the centrifugation in a conical test tube at 4 °C for 10 min/900 gr. Then the lymphocyte sludge is resuspended with a Hanks buffer and adjusted to 2-3000 lymphocytes at 3mm and is used for typing of a pre-check of cell variability.

Determination of the antigens from locus A and B is performed in 14 antigen serums for locus A and 23 antigen serums for locus B. Serums are procured commercially, and a number of typings are made with serums obtained from transplantation centre from the hospital "Rebro" in Zagreb, Croatia, as well as from our own production.

Rabbit complement is obtained by separating blood serum from 10 male non-immunized rabbits. It is examined not to be cytotoxic in itself, and if it is negative, it is used as a reagent in the test.

The test is performed by placing a 1 µL lymphocyte suspension in the plaques where the serums are different in accordance with a particular plan. After incubation for 30 minutes add 5 µL of complement at room temperature and incubate for 1 hour under the same conditions.

Then, the same substance is denatured on the plates, except the lymphocytes, and 1µL of the prepared solution of trypan blue (1% solution) is added, if the lymphocyte membrane reaction occurs, the corresponding antigen is bound to the adequate serum antibodies in the presence of complement. Autoantibodies kill the cell, i.e. the cracked membrane passes through the colour and the lymphocytes bloom and blue stain. If there is no reaction, the cells are alive with the usual size and are easily illuminated under a microscope.

Reading of the findings was performed with an inverse microscope, determining the percentage of the dead cells, from 20-50%, dead lymphocytes were 2 points, 51-80% were three points and 81-100% were four points. A positive reaction was the one when there were 3 or 4 points. The battery plans (series of different plates of the same serums) were assembled in such a way to avoid the mistakes of secret reactions by placing more serum on the same antigen or for added antigens.

Patients from the examined group and both subgroups (reticular and erosive) and the control group were compared to each other through typified HLA-antigens in locus A and B.

In patients with lichen planus and the control group in which HLA-antigenic typing was performed, the statistical analysis included determining the antigen frequency (the representation of a particular antigen, expressed in percent %) and determining a relative risk factor (RR) for possible associated antigens according to mathematical calculations.

RESULTS

In the group with the reticular form (33 patients) the antigen A2 is present in 19 (57.57%), and in the group with erosive form, the most common antigen is A9, 8 (88.88%). In the locus B in the reticular form there is B12, 7 (21.21%), and in

the erosive antigen B8 in 7 subjects with antigenic frequency 77.77%.

In locus A, the relative risk factor for the occurrence of reticular lichen planus is A3 (RR2.31, $X^2 = 9.14$) and $p \leq 0$ in the examined compared with the control group. In locus B, as risky antigens in the same group appear B36 (RR4.38, $X^2 = 4.76$) and B44 (RR 0, 17, $X^2 = 4.46$), where $p \leq 0.05$.

It is evident that from locus A in the examined in comparison to the control group A 9 (RR 3.65, $X^2 = 20.72$) $p \leq 0.001$ is obtained. As far as locus B is concerned, the antigen B8 (RR 6.7, $X^2 = 37.64$) shows a high level of A9 ((RR 3.65, $X^2 = 20.72$) and $p \leq 0.001$, significance between the investigated and the control group, $p \leq 0.001$.

Table 1. HLA-antigen typing of locus A and B in patients with reticular and erosive form of oral lichen planus.

	CLINICAL FORMS			
	RETICULAR		EROSIVE	
	N	%	N	%
A-LOCUS				
A1	6	18.18	5	55.55
A2	19	57.57	1	11.11
A3	11	33.33	1	11.11
A9	1	3.03	8	88.88
A10	4	12.12	1	11.11
A11	1	3.03	1	11.11
A26	1	3.03	-	-
A28	4	12.12	-	-
A29	5	15.15	-	-
A30+31	1	3.03	-	-
A32	1	3.03	-	-
B-LOCUS				
B5	4	12.12	3	33.33
B7	3	9.09	1	11.11
B8	4	12.12	7	77.77
B12	7	21.21	-	-
B13	4	12.12	-	-
B14	2	6.06	1	11.11
B15	1	3.03	1	11.11
B16	1	3.03	-	-
B17	3	9.09	-	-
B18	4	12.12	1	11.11
B21	1	3.03	-	-
B27	3	9.09	-	-
B35	4	12.12	-	-
B38	2	6.06	-	-
B40	4	12.12	-	-
B44	1	3.03	-	-
BS	-	-	-	-

Table 2. Factor of relative risk in typing of HLA-antigens from locus A and B in patients with reticular form and control group

	Examined group			Control group			RR	X ²	P≤
	HLA - Typified A-locus	N=33	Antigen frequency %	HLA - typified	N=1300	Antigen frequency %			
RETICULAR FORM	A1	6	18.18	A1	341	26.23			
	A2	19	57.57	A2	677	52.07			
	A3	11	33.33	A3	187	14.38	2.31	9.14	0.05
	A9	1	3.03	A9	358	27.53			
	A10	4	12.12	A10	197	15.15			
	A11	1	3.03	A11	111	8.53			
	A26	1	3.03	A26	107	8.24			
	A28	4	12.12	A28	126	9.69			
	A29	5	15.15	A29	35	2.69			
	A30+31	1	3.03	A30+31	59	4.53			
	A32	1	3.03	A32	26	2.00			
	AX	12	36.36	AX	382	29.30			
	B-locus								
	B5	4	12.12	B5	443	34.07			
	B7	3	9.09	B7	153	12.53			
	B8	4	12.12	B8	170	13.07			
	B12	7	21.21	B12	227	17.46			
	B13	4	12.12	B13	83	6.36			
	B14	2	6.06	B14	44	3.38			
	B15	1	3.03	B15	41	3.15			
	B16	1	3.03	B16	34	2.61			
	B17	3	9.09	B17	95	7.30			
	B18	4	12.12	B18	91	7.00			
	B21	1	3.03	B21	73	5.61			
	B27	3	9.09	B27	105	8.07			
	B35	4	12.12	B35	347	25.69			
	B36	2	6.06	B36	18	1.38	4.38	4.76	0.05
	B40	4	12.12	B40	125	9.61	1.29	0.22	
	B44	1	3.03	B44	319	16.85	0.17	4.46	0.05
	Bw54	1	3.03	Bw54	11	0.84	0.27	1.78	
	BY	17	51.51	BY	387	29.76	1.73		

Table 3. Relative risk factor for the typing of HLA-antibodies in locus A and B in the erosive form and the control group

	EXAMINED GROUP			CONTROL GROUP			RR	X ²	P≤
	HLA - typified A-locus	N=33	Antigen frequency %	HLA - typified	N=1300	Antigen frequency %			
EROSIVE FORM	A1	5	62.5	A1	341	26.23			
	A2	1	12.5	A2	677	52.07			
	A3	1	12.5	A3	187	14.38			
	A9	8	100.0	A9	358	27.53	3.65	20.72	0.001
	A10	1	12.5	A10	197	15.15			
	A11	1	12.5	A11	111	8.53			
	AX	1	12.5	AX	382	29.38			
	B-locus		%			%			
	B5	3	37.5	B5	443	34.07			
	B7	1	12.5	B7	163	12.53			
	B8	7	87.5	B8	170	13.07	6.7	37.64	0.001
	B12	1	12.5	B12	227	17.46			
	B14	1	12.5	B14	44	3.38			
	B15	1	12.5	B15	41	3.15			
	B18	1	12.5	B18	91	7.00			
	BY	3	37.5	BY	387	29.76			

Table 4. A summary of the relative risk of the most commonly typified HLA-antigens in the reticular and erosive form of oral lichen planus

Clinical forms	H L A - antigen	A - locus			H L A - antigen	B - locus		
		RR	X ²	P≤		RR	X ²	P≤
Reticular	A3	2.31	9.14	0.005	B38	4.38	4.76	0.05
					B44	0.17	4.46	0.05
Erosive	A9	3.65	20.72	0.001	B8	6.7	37.64	0.001

Table 4 presents a summary of the most commonly typified HLA-antigens in the reticular and erosive clinical form of the oral Lichen Planus IN LOCUS A and B. In the reticular form of locus A, typically A3 is typed with RR2.31, X² = 9.14 and the statistical significance p≤ 0.005, and from locus B, B38 (RR4.38, X² = 4.76) and B44 (RR0.17, X² = 4.46) where p≤ 0.05. The erosive form of locus A and B is usually typified A9 with RR 3.65, X² = 20.72 and the statistical significance is p≤ 0.001, B8 (RR 6.7, X² = 37.64) and p≤ 0.001.

DISCUSSION

The unknown aetiology of oral lichen planus and the modest knowledge of the possible predisposition to this disease is still a challenge for many authors to examine the relationship between certain antigens of the HLA system and this disease.

The results obtained from the literature on the possible genetic determinant of the restriction to this disease are inconsistent and contradictory.

Long time ago Watanabe [45] had proven that in patients with clinically diagnosed lichen planus the frequency of antigens from locus A and B has no significant difference. Antigen from the locus DR showed high frequency, which suggests a genetic affiliation to this disease.

In the serological classification of class II HLA antibodies in patients with established clinical diagnosis of lichen planus with oral and dermal localization Powel [17], has come to the conclusion that the antigens from the DR locus are also predominant here. Up to a similar assumption came Regezi [15] who through the use of immunohistochemical analysis studied patients with lichen planus and received the highest presence of antigens from the locus DR.

From our immediate environment, Kolevski [46] was involved in this research, and in his

study in a small number of subjects with lichen planus, regardless of the localization, oral, dermal or oro-dermal he observed an increased frequency of A3 antigen, with $p \leq 0.05$.

In this study, patients with oral lichen planus in locus A and B in the reticular and erosive form were typed. In the reticular form with the highest frequency, the antigen A3 (RR 2.31, $X^2 = 9.14$) and $p \leq 0.05$ appears. In the erosive form A9 (RR 3.65, $X^2 = 20.72$) and $p \leq 0.001$.

As for the antigens, also from locus A and B in the reticular and erosive form of high statistical significance, the B8 antigen (RR 6.7, $X^2 = 37.64$) is typified, where $p \leq 0.001$ is consistent with the results obtained from the Simon survey. [47]

The literature available to us at the time of this research was rather scarce with information related to the alloantigens in individual clinical forms of the oral lichen planus, therefore, we are unable to make a rich confrontation of our findings with the results of other authors.

A wealth of literary data is available from studies involving other diseases, as well as dermal or orodermal findings and association with antigens from the HLA - system.

Positive staining for HLA-DPDQDR in the attacked regions of the palmoplantar lichen planus (PPLP) has been demonstrated. The authors suggest the active presentation of T-lymphocyte peptides. They record T lymphocytes as well as CD3, CD8 and CD45 positive infiltrates. The authors conclude that despite the positivity of HLA-DPDQDR, PPLP, a key role has a cellular immune response in the etiopathogenesis of the disease. [48]

In addition to the fact that the association between HLA antigens and lichen planus has been studied long ago [49- 52], the idea of association continued, and the desire for proof did not go away, and in recent years researches in this area has expanded. [53-55] However, the findings were again evaluated as different. The differences were detected by many features. It is worth highlighting the differences that are due to the clinical variations of the lichen planus, localization, manifestation, but also the area where the population is examined. [56- 58]

Heterogeneity of the obtained data begins to impose the view that perhaps certain exogenous factors can influence the variety in the expression

of genes that definitely reflect on the affiliation of certain antigens to lichen planus.

The association of antigens from the HLA-system has not been tested only for patients with lichen planus, the association has been investigated with other diseases. The literature is known for findings in non-cicatrice alopecia (alopecia areata). The authors point out HLA DQB1 as the responsible gene for this disease. [59, 60] This gene is thought to be involved in pathogenic cases.

Pavlovsky et al. [61] found that DRB1 * 11: 01 and DRB1: 11:04 alleles were significantly enlarged at patients with lichen planus (LPP) and are highly related, but due to the unbalance of the connection, it was not possible to determine whether both DRB1 and DQB1 loci are involved in the pathophysiology and manifestation of LPP. There is a reasoning that LPP is associated only with one of these loci, while the other is an associated locus as part of the most commonly inherited haplotypes.

Analysing our results and comparing them with the results of other authors [4, 39, 62], we noticed a fair heterogeneity of the findings. Namely, we coincide with certain findings [41, 63], but in terms of the findings of a certain group of authors there is a discrepancy in the obtained results. [16, 44, 64]

We find that the main reason for the diversity of findings is in our small group of examinees and inability to make typing in other loci due to financial reasons. Therefore, the research was carried out only in locus A and B, while others were not taken into account.

The desire to make a research on the possible association of the oral lichen planus with antigens from the HLA system was supported by the need to clarify the unknown etiological mechanisms. Entering deeper and performing typing in locus A and B according to the clinical manifestation (reticular and erosive form), we justify it with differently detected HLA antigen in various clinical forms due to the peaceful course of the disease (reticular) and the possibility of malignancy (erosive) form. In the second form, the chances are far greater. The possible coincidence of the same HLA antigen in lichen and carcinoma would be valuable data for each clinician.

CONCLUSION

In the erosive form, the A9 and B8 antigens can be considered as predisposing antigens for the emergence and development of the erosive lichen planus $p \leq 0.001$. The reticular form in the A-locus is the antigen A3 $p \leq 0.001$.

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Резиме**ОРАЛЕН ЛИХЕН ПЛАНУС –
ПОВРЗАНОСТ СО АНТИГЕНИТЕ ОД ХЛА-СИСТЕМОТ**

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Цел: Да се утврди дали постои имуногенетска поврзаност и антигенска разлика меѓу ХЛА-антигените кај ерозивниот (ЕОЛП) и ретикуларниот (РОЛП) орален лихен планус (ОЛП).

Материјал и метод: Испитувани се 73 пациенти со РОЛП и ЕОЛП. Кај сите испитувани пациенти е направена типизација за антигените ХЛА од локус А и Б. ХЛА-типизацијата е спроведена со примена на микролимфоцитотоксичниот тест според Terasaki. Читањето на наодите е спроведено со инверзен микроскоп. Позитивна реакција е онаа што има четири поени.

Резултати: Најчесто типизирани антигени кај РОЛП од локус А се ХЛА А2 (57,57 %) и А3 (33,33 %), а во локус Б – 21,21 %. Кај ЕОЛП е А9 (88,88 %). Во локусот Б е пронајдена поврзаност со ХЛА Б8 (77,77 %). Статистичката анализа со χ^2 тестот покажа дека носителите на ХЛА А9 покажуваат релативен ризик $RR = 3,65$ и $\times 2 = 20,72$. Оттука, постои висока статистичка значајност за локус А $p < 0,001$. За локус Б, кај ЕОЛП за ХЛА Б8, $RR = 6,7$ и $\times 2 = 37,64$ и $p < 0,001$. РОЛП покажа асоцираност со ХЛА А3, каде што $RR = 2,31$ и $\times 2 = 9,14$ и $p < 0,05$.

Заклучок: Кај РОЛП А3 антигенот, а кај ЕОЛП А9 и Б8 може да се сметаат како носители кон predisпозиција за ОЛП.

Клучни зборови: орален лихен планус, ерозивен, ретикуларен, ХЛА, сквамозно-клеточен карцином