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Professor VLADIMIR LESOVOY

Rector of Kharkiv National Medical University
Corresponding Member of the National Academy of Medical Sciences of Ukraine
Laureate of the State Prize of Ukraine in Science and Technology
Honoured Doctor of Ukraine

Dear readers of "The New Armenian Medical Journal"!

I am very pleased to present the publications of the staff of Kharkiv National Medical University in such an authoritative medical edition as "The New Armenian Medical Journal".

Kharkiv National Medical University is one of the oldest higher medical schools in Ukraine, which is now preparing to celebrate its 215th anniversary. Our University traces its history from the medical faculty of the Imperial Kharkiv University, founded in 1804.

Kharkiv National Medical University has served the development of medical science and practice, striving for the best quality of education and research.

In the list of the names that created the history of our University, there are the names of professors I.I. Mechnikov, V.F. Groube, L.L. Girshman, A.G. Podrez, I.P. Lazarevitch, V.Ya. Danylevsky, N.S. Bokarius, M.P. Trinkler, V.P. Vorobyov, A.M. Gasparyan, L.A. Oganesyan, L.T. Malaya, V.I. Grischenko, A.A. Shalimov and many others, who made a significant contribution to world medicine and brought well-deserved fame to Kharkiv. These professors of the Faculty of Medicine of Kharkiv University were the first who performed such surgeries as ovariotomy, definitive resection of stomach, open heart surgery, and made significant scientific discoveries in the Russian Empire.

Today, Kharkiv National Medical University is a modern multi-discipline educational institution with a strong scientific, material and technical base. Our University has six educational research and production associations, seven educational, scientific and scientific-practical centres: Training and Research Medical Complex "The University Clinic", Research Institute of Occupational Hygiene and Occupational Diseases, Medical Training and Research Division "The Dental Centre", Medical College, Scientific and Practical Centre for Preclinical and Clinical Trials, Centre for Gender Education and Centre for Medical Regional Studies, etc.

The University has 70 departments. The University staff counts 933 academic and research professionals, including 116 professors, 72 associate professors, 129 doctors of medical science and 543 candidates of sciences (PhDs). Among them there is one academician of the NAMS of Ukraine, five corresponding members of the Ukrainian National Academy of Sciences, 15 Honoured Workers of Science and Technology of Ukraine, 15 Honoured Doctors of Ukraine, Honoured Worker of Pharmacy of Ukraine, three Honoured Workers of Education of Ukraine, nine laureates of the State Prize of Ukraine in Science and Technology, 19 academicians of state and public academies of Ukraine.

Over the period of KhNMU's existence, more than 62.000 doctors have been trained in its walls.

Currently, more than 7.000 students are studying at the University, including more than 3.000 foreign citizens from 82 countries. KhNMU was one of the first in Ukraine (1951) to start training medical personnel for different countries of the world. Over this period, the University has trained more than 3.600 professionals for 86 countries in Western Europe, Asia, Africa, Latin America, the Middle East, including three doctors of sciences and 70 candidates of medical science, more than 250 clinical residents.

The University is proud that its alumni were and continue to be the elite of their countries. Among the students of Kharkiv Higher Medical School: 34 academicians and corresponding members of various academies of sciences, six Heroes of Labour, Heroes of Socialist Labour and Heroes of Ukraine, 34 laureates of State Prizes, 23 ministers and heads of government authorities, 67 directors of research institutes and centres, 31 rectors of higher education institutions, 17 deputies of the Supreme Council of Ukraine, and six honorary citizens of Ukrainian cities.

Throughout the history of the University, international educational and scientific cooperation were one of the priorities of its activity. It included cooperation with educational and scientific institutions, with international organizations, publishing houses and scientific journals. We are very pleased that the authoritative edition of the Yerevan State Medical University after Mkhitar Heratsi "The New Armenian Medical Journal" has become our good partner and friend. I would like to congratulate the founders and editorial staff of the journal, represented by the Rector of the Yerevan Medical University after Mkhitar Heratsi, Professor Armen Muradyan and the Editor-in-Chief Professor Arto Zilfyan, with the 10th anniversary of "The New Armenian Medical Journal". I want to wish respected colleagues new interesting publications, a large number of interested readers, further leadership positions among international medical editions, peace and prosperity!

Professor VALERIY MYASOYEDOV

Vice-Rector for Research of Kharkiv National Medical University
Honoured Worker of Science and Technology of Ukraine

Dear readers of "The New Armenian Medical Journal"!

I am glad that the current issue of the journal includes the articles by the leading scientists of Kharkiv National Medical University. They demonstrate the mainstream of scientific research carried out at our University. These articles are devoted to topical issues of therapy, pediatrics, urology, nephrology, dentistry, pathological anatomy and public health, those branches of medical science and practice which today, as always, determine the trend in the development of medicine.

Research work is an important aspect of Kharkiv National Medical University's activities, which in integration with educational activities is aimed at training highly qualified personnel and solving urgent problems of medical science and the healthcare system.

Today, among the priority areas of scientific research at the University are the prevention, diagnosis and treatment of cardiovascular diseases; minimally invasive interventions in acute and chronic pathology; prevention, diagnosis and treatment of viral, bacterial infections based on the study of their pathogenetic mechanisms, etc.

At the University, 15 scientific and pedagogical schools have been formed, and they are successfully developing now. These are anatomical, pathoanatomical, histological, physiological, biochemical, pathophysiological, surgical, hygienic, pediatric, therapeutic, microbiological, urological, obstetric-gynecological, neurological, psychiatric and pharmacological schools.

At present, the University carries out 60 scientific research works. Annually, the University's staff receives about 80 patents, including more than 20 ones for inventions. About 800 reports are presented at scientific forums in Ukraine, about 150 - in the CIS countries, about 200 - in the countries of the far abroad. Printed scientific materials are about 40 monographs annually and about 2.000 publications in scientific editions.

Kharkiv National Medical University ranks 26th among all universities and 5th among higher medical education institutions in Ukraine in terms of Scopus scientometric database. Annually, about 50 scientific forums, including international ones, are held at the University and with its participation. The University provides doctoral training, postgraduate training and clinical residency in more than 40 specialties, 48 doctoral and 235 PhD dissertations are being carried out.

There are five specialized scientific councils for the defense of doctoral theses and dissertations for the degree of PhD in 16 specialties at the University. The University scientists actively cooperate with many foreign and international research institutions and organizations, in particular with the Federation of European Physiological Societies, the European Association of Urology, the European Society of Human Reproduction and Embryology, the European Society of Uroradiology, the International Brain Research Organization, the WHO Regional Office for Europe, the American Medical Research Foundation and others.

Today, the key to success in any field of human activity, science in particular, is effective communication. Scientific journals are the cornerstone of such communication. I am very pleased to congratulate honorable colleagues from Yerevan State Medical University after Mkhitar Heratsi, the editorial staff and its Editor-in-Chief Arto V. Zilfyan on the 10th anniversary of "The New Armenian Medical Journal", a beautiful star on the scientific horizon. I want to thank my dear colleagues for their friendship, mutual understanding, high publishing competence and I would like to wish you a lot of anniversaries ahead, new embodied ideas, peace and good!

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THE ROLE OF NITRIC OXIDE SYNTHASE IN THE MODULATION OF THE IMMUNE RESPONSE IN ATOPIC DISEASE

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Abstract

Present study aimed to determine the effect of endothelial and inducible nitric oxide synthase on the inflammatory process of soft tissues in the oral cavity of experimental animals in the modulation of atopic disease. To simulate the atopic process, young experimental animals (three-month-old male rabbits) were sensitized by intraperitoneal injection of ovalbumin and aluminum hydroxide during the first 3 days of the experiment. Twice lower dose of ovalbumin was instilled intranasally under local anesthesia five days later (Day 8) with repeated intranasal administration of ovalbumin on the 16th, 17th, 20th and 21st day of the experiment. Obtained specimens of oral cavity were examined histologically, and immunohistochemical study was performed to determine the immunoreactivity of eNOs, iNOs, CD23, CD20.

Histological investigation of obtained microslides detected that atopic modeling process is implemented by a complex of pathological changes of oral mucosa with the presence of intraepithelial lymphocytes, eosinophils, focal erosive lesions, signs of proliferation of the basal cell layer, moderately expressed papillomatosis. Such histological picture can be interpreted as the development of inflammatory, degenerative, dyscirculatory process. It was found that such changes are accompanied by disturbance of nitric oxide synthase metabolism, characterized by increased activity of inducible nitric oxide synthase more than twice and endothelial synthase in the extravascular space. Inflammatory infiltrate in atopic process is presented by B-lymphocytes, activated macrophages, eosinophils both in the lamina propria and epithelium that is indicated by a sharp increase in the immunoreactivity of CD23 and CD20. Accumulation of these cells has strong correlation dependence with nitric oxide synthase. The most pronounced correlation has been detected between CD23 and CD20 (r=0.89), iNOs and CD23 (r=0.85), iNOs and CD20 (r=0.87) while comparing the results of immunohistochemical study with eNOs, iNOs, CD23, CD20. The obtained data can be used as a basis for the development of preventive measures in patients with atopic diseases, based on the correction of disturbed nitric oxide metabolism.

Keywords: *atopy, nitric oxide synthase, experiment, oral cavity, inflammation.*

Introduction

Atopic conditions are characterized by inherited peculiarity to produce immunoglobulin E antibodies as a response to small amounts of common environmental proteins such as pollen, house dust mite and food allergens [*Thomsen S, 2015*]. Today, many aspects of the development of bronchial asthma, allergic rhinitis and atopic dermatitis remain unexplored, and there is a necessity for further experimental studies to clarify the pathogenesis of atopic diseases and creation of primary prevention and pathogenetically based treatment of patients suffering from atopic diseases including their clinical manifestations in oral cavity [*Staab D et al., 2006; Thomas M et al., 2010*]. As the frequency of atopic dermatitis in children is about 15% [*Scharschmidt T, Segre J, 2008; Krivenko L, Nazaryan R, 2015*], and the presence of this pathology entails the increase of carious lesions [*Bezruk V et al., 2015*], the study of the pathogenesis of atopic changes becomes a goal not only for allergists, internists, pediatricians, but also for dentists.

One of unclear aspects in the pathogenesis of

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atopic processes remains the disturbance of nitric oxide metabolism with its involvement in the immune processes, including the processes in the oral cavity [*Everekliogl u C et al., 2002; Yildirim M et al., 2004*].

Present study aimed to determine the effect of endothelial and inducible nitric oxide synthase on the inflammatory process of soft tissues in the oral cavity of experimental animals in the modulation of atopic disease

Material and methods

In order to study the morphofunctional state of the tissues of the oral mucosa in atopic disease, an experimental study was carried out, that allows to eliminate the influence of somatic pathology and social factors. Ovalbumin was used to simulate atopic process according to the previously proposed and widely used scheme [*Yoshida M et al., 2002; Cho S et al., 2008; Kim H et al., 2014*]. To simulate the atopic process, young experimental animals (three-month-old male rabbits) were sensitized by intraperitoneal injection of ovalbumin and aluminum hydroxide during the first 3 days of the experiment. Twice lower dose of ovalbumin was instilled intranasally under local anesthesia five days later (Day 8) with repeated intranasal administration of ovalbumin on the 16^{th}, 17^{th}, 20^{th} and 21^{st} day of the experiment. Doses of used medicine were determined according to animal body weight. We formed two groups with 8 animals each – intact animals and group of animals with simulated atopy. Two groups with 8 animals each were formed – group of intact animals and group of animals with simulated atopy.

The specimens of soft tissues of the oral cavity were stained with hematoxylin and eosin, picrofuxine according to van Gieson after the routine proceeding. Immunohistochemical study was performed by indirect immunoperoxidase reaction with monoclonal antibodies to endothelial and inducible NO-synthase fractions (eNOs and iNOs, respectively), CD23 (detected on mature B cells, activated macrophages, eosinophils, has affinity with immunoglobulin E [*Kijimoto-Ochiai S, 2002*]), CD20 (coreceptor located on the surface of all B-lymphocytes [*Janas E et al., 2005*]). All used monoclonal antibodies are manufactured by Thermo Scientific (USA). The reaction was visualized using a set of UltraVision LP Detection System HRP Polymer & DAB Plus Chromogen (Thermo Scientific, USA). All microspecimens were performed in the Department of Pathological Anatomy of the Kharkiv Medical Academy of Postgraduate Education.

The microslides were studied using "Olympus BX-41" microscope (Japan) with subsequent processing by "Olympus DP-soft version 3.2" software (Japan), which was used both for definition of the intensity of immunohistochemical reactions and for morphometric study. The intensity of immunohistochemistry was analyzed by detecting the optical density of relevant morphological structures in conventional unit. Morphometric study was performed by overlaying a grid with a square cell (side 10^{-4} *m*) and detecting the density of cellular elements of inflammatory series, including the immunopositive staining of CD23, CD20.

Statistical analysis of the study results was performed on a personal computer using Microsoft Excel and Statistica-10 database software. The criteria of non-parametric statistics were used in order to assess the significance of differences in sample populations. Statistical comparison was performed using Mann-Whitney test for statistical analysis. Spearman's rank correlation coefficient (r) was counted for measure of the strength of a relationship between paired data. The accepted level of significance was $p<0.05$.

The study was approved by Institutional Bioethics Committee and conforms to the principles of the Guide for the Care and Use of Laboratory Animals published by US NIH (No 85-23, revised in 1985).

Results

Histological investigation of obtained microslides detected that atopic modeling process is implemented by a complex of pathological changes of oral mucosa. Squamous epithelium is characterized by uneven thickness with the presence of intraepithelial lymphocytes, eosinophils, focal erosive lesions (Fig. 1), signs of proliferation of the basal cell layer, moderately expressed papillomatosis.

Perivascular inflammatory infiltrates, diffuse distribution of eosinophils, swelling of connective tissue fibers have been revealed in the lamina propria. Microcirculation is characterized by uneven blood supplying with the presence of predominantly dilated vessels.

Immunopositive tissue to eNOs is detected primarily in the wall of the microvasculature both in the study group and the group of intact animals. Whereby, longitudinal and transverse sections of vessels in both groups of animals are characterized by eNOs accumulation primarily in the endothelium. At the same time the group of animals with simulated atopy, eNOs immunoreactivity is detected between the vessels, while such pattern is observed in the lamina propria and underlying muscle plate (Fig. 2).

Determination of the optical density of the dyestuff accumulation indicates that the activity level of eNOs did not significantly differ in the vascular wall of experimental animals of both groups, while extravascular localization of eNOs is significantly higher in the group of animals with simulated atopy (Table).

More significant differences are identified while comparing the results of peroxidase reaction with iNOs. So, more pronounced rate has been revealed in the group of rabbits with the modeling of atopy that is morphometrically confirmed by almost double growth (Table). In this case there are areas both with diffuse and focal immunopositive amplification of stained tissues. The presence of local zones of increased immunoreactivity led us to assume that such changes could be the result of the activation of inflammatory cells. The fact of most active iNOs localization around the inflammatory cells in epithelial layer (Fig. 3) and in the lamina propria could be used as evidence of such immunomodulatory interactions.

Most pronounced activity of iNOs had been detected in the affected areas of the lamina propria and was associated with perivascular inflammatory microinfiltration, and the level of immunoreactivity intensity was associated with the quantitative and qualitative composition of the cellular infiltration into tissues in atopy.

Study of the density of cellular elements with immunoreactivity to monoclonal antibodies of CD23 protein was interesting as it is protein, which, as stated above, is detected on mature B-cells, activated macrophages, eosinophils, and that is important for studying atopic process, has affinity to immunoglobulin E. It is established that such elements in the group of intact animals are found as single cells in the lamina propria. In the group

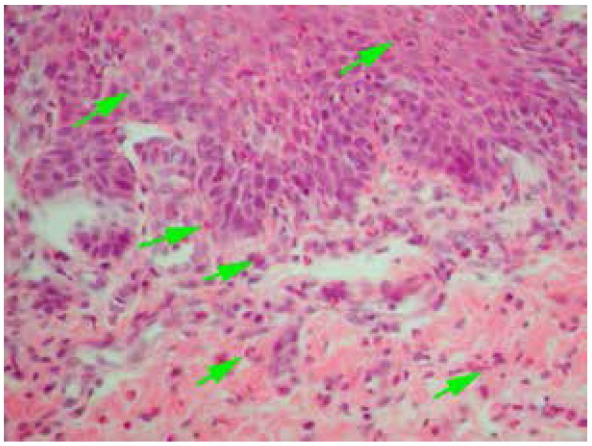

FIGURE 1. Uneven thickness of squamous epithelium with the presence of intraepithelial lymphocytes, eosinophils (indicated by arrows), proliferation of basal layer cells. The presence of perivascular inflammatory infiltrates with eosinophils and their diffuse distribution in the lamina propria, swelling of connective tissue fibers. Hematoxylin and eosin stain. Objective ×40

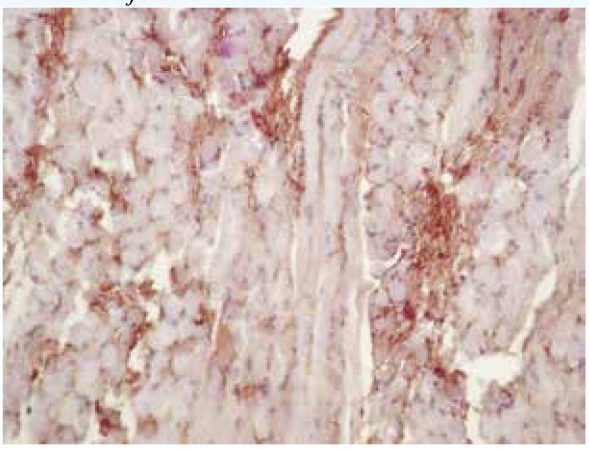

FIGURE 2. Localization of eNOs is observed not only in the microvasculature, but in the perivascular space of lamina muscularis mucosae. Peroxidase reaction with monoclonal antibodies to eNOs. Objective x20

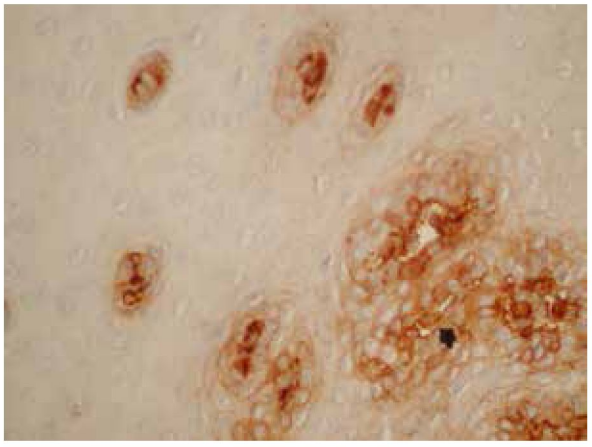

FIGURE 3. Pronounced activity of iNOs around the inflammatory cells including those located intraepithelially. Peroxidase reaction with monoclonal antibodies to iNOs. Objective ×40

TABLE

Morphometric indicators of the activity of immunohistochemical reactions

Groups	eNOs in vascular wall (*c.u.*)	eNOs of extravascular localization (*c.u.*)	iNOs (*c.u.*)
Intact animals	0.899±0.061	0.193±0.05	0.241±0.052
Animals with simulated atopy	0.793±0.112 1	0.271±0.041*	0.499±0.073*

Note: ** – $p<0.05$ compared to the intact animals*

of animals with simulated atopy their distribution differs both qualitatively and quantitatively. First of all, almost all intraepithelial inflammatory cells were positive to CD23. Majority of the cellular elements were also proved to be immunopositive to CD23 in the lamina propria, where the density of cells with CD23 nuclear staining was 7.7 times higher than in intact animals.

When studying the distribution of CD20 (the co-receptor located on the surface of B-lymphocytes), changes are found that are qualitatively similar to those observed in the study of CD23 (the appearance of immunopositive cells in the epithelium and a sharp increase in their number in the propria of the mucosa) with membrane localization of the dye.

Studying of CD20 distribution (co-receptor located on the surface of B-lymphocytes) revealed qualitatively similar changes to those observed while studying CD23 (appearance of the immunopositive cells in the epithelium and a sharp increase in the number of lamina propria) with membrane substance localization. Comparison of the CD20 cell density of intact animals and animals with atopy showed an increase of 8.9 times.

Comparison of the immunohistochemistry results for eNOs, iNOs, CD23, CD20 revealed the most pronounced correlation between CD23 and CD20 (r=0.89), iNOs and CD23 (r=0.85), iNOs and CD20 (r=0.87).

DISCUSSION

Increased activity of nitric oxide synthase in oral mucosa in atopic process noted in our work is combined with previously published data about increasing NOs in the skin in atopic dermatitis [*Kubo M et al., 2005*], allergic conditions [*Ten Broeke R et al., 2006*]. Thus, our Japanese colleagues [*Kubo M et al., 2005*] indicate an increase of both fractions of nitric oxide synthase in the skin in atopic dermatitis, including eNOs in the vascular wall, whereas in our study, we observe a slight decrease of this parameter. At the same time, M. Kubo and co-authors [*Kubo M et al., 2005*] hypothesize about metabolic pathways of NO in atopic skin lesions, in case of hyperplasia of the epidermis, the suppression of neuronal NOs expression realized in reducing NO production. In the dermis, activity of eNOs and iNOs is increased with NO production mainly due to the formation of reactive nitrogen forms, which leads to the formation of nitrotyrosine. In general, it can be argued on a similar picture of changes in nitric oxide synthesis in atopic states by activating primarily iNOS, in particular, the same pattern as in this study in the oral mucosa, as in the cited above work in the skin, in nasal mucosa in allergic rhinitis [*Kawamoto H et al., 1999; Oh S et al., 2003*]. Considering the identified strong correlations between CD23 and iNOS, iNOS and CD20, it can be argued on the active participation of nitric oxide in the modeling of humoral inflammatory response, which is the main process in the atopic process development [*Thomsen S, 2015*]. A special feature of present study is identification of NOs not only in mast cells, which are considered the main place of production of nitric oxide synthase [*Gilchrist M et al., 2004; Yip K et al., 2008*].

Simultaneously, there are available data about enhancing communication of iNOs activity not only with inflammatory cells, but also with cytokeratin-positive cells [*Kawamoto H et al., 1999*]. Immunoreactivity of iNOs occasionally was detected in relatively large mononuclear cells for non-epithelial populations staining with cytokeratin negative, while the majority of other cells including neutrophils and small lymphocytes are characterized by the absence of iNOs reaction [*Kawamoto H et al., 1999*]. The last one, taking into account the distribution of the CD20 and CD23 proteins, is also combined with obtained results.

Thus, we have described the morphological changes in the tissues of the oral mucosa which are usually regarded as a manifestation of atopic process with the development of inflammatory, degenerative, dyscirculatory processes, metabolic disorders, development of which has been involved actively disturbance of nitric oxide metabolism and which can serve as a basis for the development of preventive measures in patients with atopic diseases based on the correction of violations of nitric oxide.

CONCLUSION

Atopic process in the oral cavity is characterized by morphological picture with inflammatory, degenerative, dyscirculatory changes which are accompanied by disturbance of nitric oxide synthase. The activity of inducible nitric oxide fraction is increased more than twice in the oral mucosa.

In case of atopic processes in the oral cavity, the morphological picture is characterized by inflammatory, degenerative, dyscirculatory changes accompanied by disturbance of nitric oxide synthase. The activity of inducible nitric oxide fraction in the oral mucosa is increased more than twice.

Accumulation of inflammatory infiltrate in atopic process presented by B-lymphocytes, activated macrophages, eosinophils, has strong correlation dependence on the activity of inducible nitric oxide fraction.

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