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MUCOUS MEMBRANE OF THE ORAL MUCOSA ON THE MODEL OF COMPLICATIONS OF HIGH-DOSE RADIATION AND CYTOSTATIC CANCER THERAPY OF THE OROPHARYNGEAL REGION

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Absrtact

The relevance of the investigation is connected with the fact that despite all the achievements and efforts of oncological morbidity of population of the Russian Federation is growing steadily. A high level of disability and mortality among patients of an oncological profile cause significant socio-economic damage to the state and it requires further search for methods and means to improve the quality of the treatment. The incidence of mucositis in high-dose cancer therapy is 40 to 100% so it is necessary to conduct further investigation of the pathogenesis of the disease to optimize prevention of its complications. The morphology and histophysiology of the buccal mucosa were studied in experimental modeling of iatrogenic complications of radiation and chemotherapy of malignant lesions of the oropharyngeal area. An experimental model of mucositis was created in laboratory with white rats; selected immunohistochemical markers and worked out reaction protocols; the patterns of morphological rearrangement of the buccal mucosa and histophysiological changes in its cells by the immunohistochemical method were revealed; the prospects for further work are determined. During the immunomorphological study, a number of patterns of epithelial damage were established. During irradiation and chemotherapy, there is a violation of the diffusion capacity of the basement membrane and a decrease in its area due to smoothing of the natural relief, accompanied by dystrophic processes, ulcerative and necrotic damage, hypersecretion of the mucous end parts of the small salivary and sebaceous glands. During the immunomorphological investigation, it was established that as a result of irradiation, the cheek mucous membrane of rats is characterized by dystrophic processes due to increasing tissue hypoxia and the induction of Fas-receptor of dependent apoptosis, which will lead to a progression of alternative oxidative processes inevitably: erosion, ulceration and the spread of inflammatory infiltration with a tendency to chronicity.

Keywords: *oralmucosa, iatrogenicpathology, chemotherapy, radiationtherapy, morphology.*

Introduction

The relevance of the investigation is connected with the fact thatdespite all the achievements and efforts of oncological morbidity of population of the Russian Federation is growing steadily. A high level of disability and mortality among patients of an oncological profile cause significant socio-economic damage to the state and it requires further search for methods and means to improve the quality of the treatment [*Gvozdikova E, 2017; Maria OM, 2017; Arzukanyan AV, 2020; Pulito C, 2020*].Nowadays the detection and cancer treatment in the early stages of the development is faced significant difficulties due to the large polymorphism of the clinical manifestations of tumors, age-related features, and

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the dependence of the diagnosis of malignant neoplasms on the growth dynamics, localization, local and general changes [*Tkachenko P et al., 2016;Nersesyan AK, 2018;Kusiak A, 2020*]. The oral cavity is a complex ecological system in which external factors interact with internal ones.All components of the oral system are in the dynamic equilibrium as everything is in the environment [*Yessayan L, 2017*]. Inflammation of the oral mucosa in individuals after a specific treatment for oropharyngeal head and neck cancer and in the case of iatrogenic radiation injury or its combinations withthe cytostatic therapy complications belong to the category of mucositis. According to the established risk factors for the development of the disease (15.2%) and pathological changes in the oral mucosa (17.8%) revealed a low motivational activity among patients to preventive examinations (1% – 1 year, 7.8% – 1 every 6 months) [*Bertolini M, 2017; Gnatovskaya N, 2019*]. The incidence of mucositis in high-dose cancer therapy is 40 to 100% so it is necessary to conduct further investigation of the pathogenesis of the disease to optimize prevention of its complications [*Shankar A, 2017; Tkachev S, 2017; Sobue T, 2018*]. Oncology is constantly improving approaches to chemotherapy, surgery and radiation exposure, which is one of the most important elements of treatment. Their evolution follows the path of increasing the effectiveness of action on tumor cells, proportionally increasing the destructive effects on non-tumor elements of the body's tissues. The most sensitive to damage among healthy cells are rapidly dividing epithelial cells of the oral cavity.

Currently it is becoming more common in pathogenetic studies mucositis research is gaining the molecular genetics paradigm of the scientific approach. In the diagnosis not classical morphology plays a major role, and immune histochemical method as an antigen-antibody reactionwhich is implemented in the tissue. It is unlike other molecular immunological techniques it is promising one foridentification of proteins which are signal markers for establishing their histotopographic localization in cells. The method allows translating the qualitative into the quantitative reaction to calculate the digital and biostatistical parameters forassessing the proliferative activity of cells, their metabolic characteristics, the qualitative composition of the inflammatory infiltrate[*Riley P, 2017; Kashirin VA, 2018; Zima D et al., 2019*]. These methods are the most promising in experimental works for standard investigation objects– laboratory rodents. The purpose of the investigation is to investigate the morphology and histophysiology of the cheek mucosa during experimental modeling of iatrogenic complications of radiation and chemotherapy of malignant lesions of the oropharyngeal region.

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

The accumulation of knowledge of the pathophysiological patterns of the development of mucositis in the oral cavity develops adequate approaches to pathogenetic therapy in terms of choosing from existing or developing new drugs. The classical approach explains that mucositis develops starting from the molecular level of DNA damage in cambial epithelial cells of the basal layer. This basic pattern of iatrogenic injury from aggressive cancer therapy is multi-stage. The release of reactive oxygen species is the main causative factor for damage. Damage to DNA molecules blocks information processes and the synthesis of encoded enzymes. Stopping the intracellular synthesis of plastic elements, impaired division and physiological regeneration of the epithelium with a high rate of recovery in vivo with chemotherapy and radiation therapy causes ulceration. Microbial imbalance, leukopenia and immunosuppression can provoke combined mucosal infection. Severe tissue damage is possible up to extensive ulceration and disseminated infectious lesions. The extracellular matrix plays a significant role: proinflammatory cytokines are produced by elements of connective tissue and appear to be inflammatory mediators that initiate both pathological and reparative processes. Prediction of the symptoms of oral mucositis in patients with oral mucosa cancer is based on many criteria. A two-way relationship of psychosomatic parameters with the qual-

ity of inflammation and blood coagulation, genetic predisposition and the level of sanitation of the dento-jaw system, and genetic factors is shown. At the same time, reliably individual characteristics of pathogenesis for a particular patient can be established by the immunohistochemistry (IHC) method during morphological verification of the diagnosis. When establishing the universality and commonality of processes, the revealed patterns of functional rearrangements of the epithelium will serve as the basis for correcting the recommendations of preventive tactics and treatment.

In connection with this goal, the research tasks were formulated: to create an experimental model of mucositis in laboratory white rats; to select IHC markers and work out reaction protocols; to identify patterns of morphological rearrangement of the cheek mucosa and histophysiological changes in its cells by the IHC method; to get ahead of the prospects for further work.

Material and methods

The studies were conducted on 20 male laboratory white rats Ratus Norvegicus Wistar line with a body weight of 98-108 *g*at the age of 3 months. Radiation mucositis was simulated using the IGUR-1 gamma installation with a source of 137Cs gamma-quanta in the Crimean Republican Oncological Clinical Dispensary named after V.M. Efetova. Animals were placed in a polypropylene container 8 *mm* high, 12 *mm* wide and subjected to cranial irradiation at a dose of 6 *Gy* at a power of 21.07 *Gy/min*. Then Cisplatin was administered once subcutaneously: 0.3 *ml* was diluted in 0.4 *ml* of a 0.9% NaCl solution. Mostly, clinical signs of mucositis from the digestive canal appeared on day 6-8.During this period it was taken a biopsy of the mucous membrane of the left cheek.During the experiment we followed the requirements of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes", as well as the "Rules for the Work Using Experimental Animals".

Sample preparation for immunomorphological studies was carried out according to standard methods [*Korzhevsky D,Gilyarov A, 2010*].At the LEEC ltd cutting station (Great Britain), the cheek was pulled from anesthetized animals and a fragment of the mucous membrane was cut with a scalpel from the inside, 0.5 * 0.5 * 0.2 *cm* in size. It was fixed in a 10% solution of buffered neutral formalin (Leica, Germany) onno more than 18 hours followed by standard wiring and paraffin impregnation in the LOGOS processor (Mielstone, Italy) according to the protocol recommended by the manufacturer. Leica EG 1150 N filling station (Leica, Germany) was used for concluding in paraffin and manufacturing blocks.On a Leica RM 2255 automatic microtome (Leica, Germany), paraffin sections of 4-5 μm were made. Sections were contrasted with a staining kit, including Gill's hematoxylin and Bio Vitrum Company's eosin (Russia); staining was performed according to the instructions.Microphotographs were obtained using a Leica DM2000 microscope with Planx10 and x40 lenses and an Aperio Leica Scan Scope CS2 histoscanner (Leica, Australia) at x40 magnification.

The semi-closed type immunohistostiner Bond ™ -maX was used for performing the antigen-antibody reaction automatically in tissue on paraffin sections mounted on Leica adhesive glasses, followed by dewaxing and carrying out the all steps reaction in the device according to the instructions for the immunostuner and antibodies.

One section from each block was stained with hematoxylin and eosin, and 5 tissue sections were stained with the IHC method.For visualization, a NovolincPolimer Detection System polymer detection system (Leica, Germany) was used.In order to control the method in the round of staining of experimental samples, the reactions were set for using positive and negative tissues which were served as standards.

The dynamics of mitotic proliferative epithelium activity, the apoptosis activation during the wound healing are determined by the expression level of the Ki-67 proliferation marker (MM1, Novocastra, UK), the membrane marker of cell readiness for apoptosis FAS-R (ab 82419, Abcam, USA, 1: 200 dilution) and protein-bcl-2 apoptosis inhibitor (apoptosisregulator NCL-L-bcl-2, Novocastra, UK, 1: 200 dilution), p53 apoptosis regulator protein (NCL-L-p53-DO7, Novocastra, UK, 1: 800 dilution).Evaluation of these markers with cyto-

plasmic localization was carried out by the semi-quantitative method.It wasused the following scale: 0 - no staining, or weak / medium staining of less than 25% of the cells;1+ - low-intensity staining of more than 25% of cells, or staining of strong intensity less than 25% of cells;2+ - 25-75% of the cells have medium intensity staining, or 25-50% of the cells are highly intensely stained;3+ - more than 75% of the cells are medium-intensively stained, or more than 50% of the cells are highly-intensively stained. Monoclonal antibodies detecting the macrophage marker CD 68 were used to study the intensity of inflammation (NCL-L-CD68, Novokastra, UK, 1: 200 dilution). The reaction was evaluated in the light field at a magnification of 400x in ten fields of view, counting the number of immunopositive cells it was determined the average values. The degree of tissue hypoxia was evaluated using the HIF1a marker, it was used the rabbit monoclonal antibodies HIF-1alpha (clone EP118, EptiMics, USA, dilution 1: 150).

The research results were mathematically processed using the Microsoft Excel program.For statistical processing of the obtained data it was used both parametric and nonparametric methods.The normal distribution was assessed by the Shapiro-Wilk criterion.Under thenormal distribution it was calculated the mean value, the mean-square deviation, and the mean error.It was compared the significance of differences of the sign between the separate groups using Student's t-test.It was used the Mann-Whitney U-test in the case of the deviated distribution from normal and for semi-quantitative indicators.The differences were considered statistically significant when the significance level is 5% according to the Student table ($p<0.05$, 95% is the corresponding confidencelevel).

RESULTS

The morphological and histophysiological featuresofmucous membraneof the internal cheeks surface of white rats have a number of features in normal conditions.It topographically refers to the lining (or integumentary) type.Since this is the external oral cavity (vestibulum), it can be damaged and under the influence of microbial aggression, but it is well hydrated due to abundant liquid excretion from the ducts of the parotid glands.The thick epithelial layer of the mucosa covers its own plate, passing without a sharp border into the submucosal base of the cheek, bordering on voluntary muscles in the absence of muscle plate of mucous membrane.The epithelium is represented mainly by the non-keratinizing type (Fig. 1A).

The cambial basal layer of epithelial cells is connected by tonofilaments and desmosomal contacts.These basophilic cells of small volume have large dark nuclei with condensed chromatin in the form of clumps, a high nuclear-cytoplasmic ratio, they actively divide, especially in the areas of the apices of epithelial scallops. In the parabasal layer the cells become larger, the volume of the cytoplasm increases, the nucleus are getting brighter, chromatin looks like dust, cells take a prickly or angular shape (Fig. 1B).

In the future cells differentiation and migration

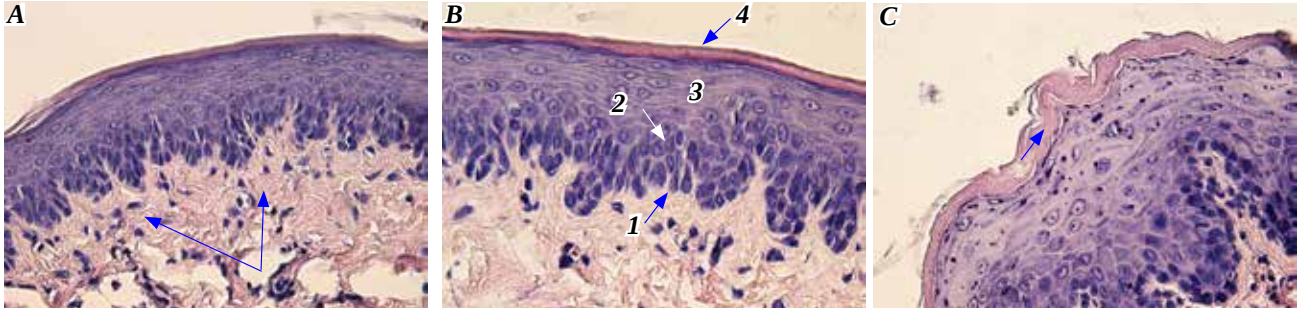

FIGURE 1. *The control. A fragment of the mucous membrane. Hematoxylin and eosin stain.*
(A)*. with a thick layer of integumentary stratified squamous epithelium, deepening in the form of epithelial scallops into the connective tissue base (arrows), which forms the papilla. SW 100x*
(B) *with formed layers of epithelial cells: basal, parabasal, intermediate and superficial (1, 2, 3, 4, respectively). SW 100x*
(C) *with formed epithelial scallops and connective tissue papillae. Above the layers of epithelial cells: basal, parabasal, intermediate and superficial, a layer of cells with karyopyknosis, karyorexis and karyolysis is highlighted (parenthesis), passing into the eosinophilic stratum corneum (arrow). SW 400x*

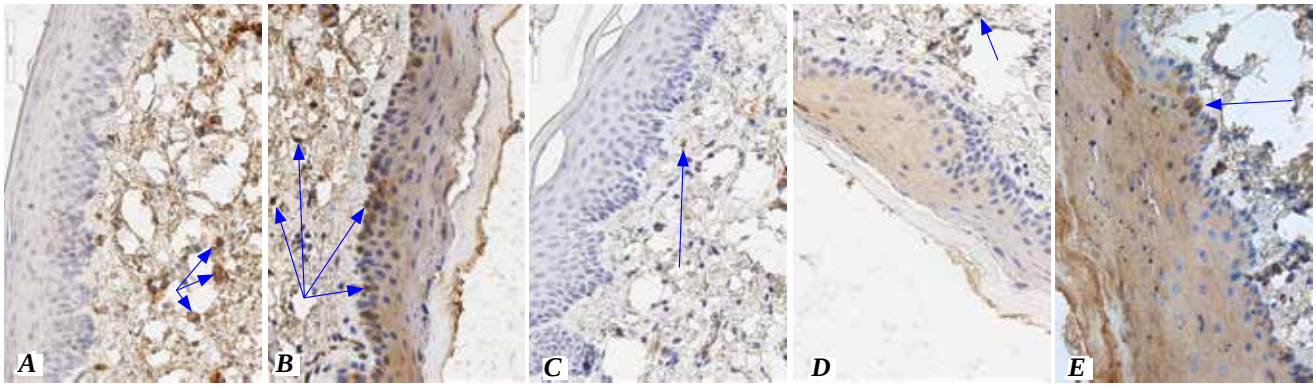

Figure 2. *A fragment of the cheeks mucous membrane. The control.*
(A) *– CD-68 + macrophages with cytoplasmic expression in the submucosal layer (arrows). IIH. SW 400x.*
(B) *– CD-95 + (FASR) cells in the basal and parabasal layers of the epithelium as well as they are in the submucosal layer (arrows). IHC. SW 400x.*
(C) *– Single p53 + cells in the submucosal layer (arrows). IHC. SW 400x.*
(D) *– Single bcl-2 + cells in the submucosal layer (arrows) and moderate background staining of the epithelium. IHC. SW 400x.*
(E) – Strengthening HIF reaction as removing from the basement membrane in the epithelial layers of the mucous membrane with a single pronounced reaction in the basal layer (arrow). IHC. SW 400x.

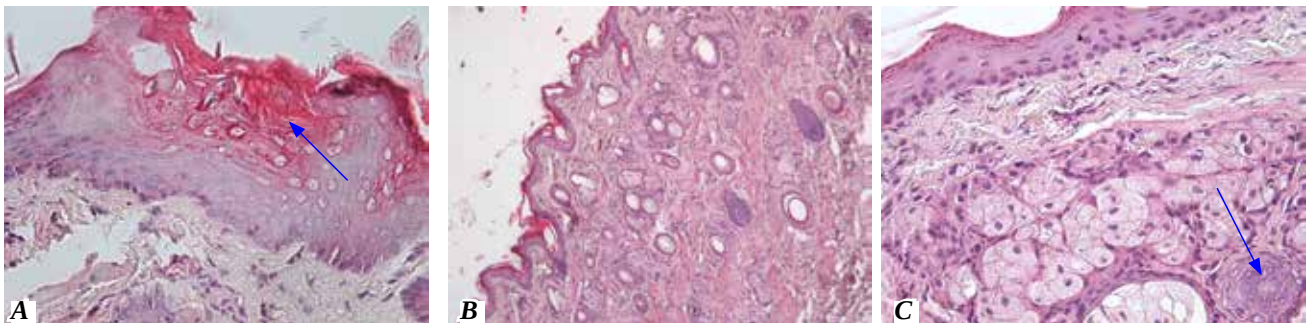

Figure 3. *Radiation and chemotherapy.*
(A) – A fragment of the mucous membrane with an epithelial defect (arrow), connective tissue papillae are uneven, smoothed, semicircular, penetrate into the epithelial layer only 1 / 8-1 / 10 of its thickness, single pointed, deeper papillae of the lamina propria. Hematoxylin and eosin stain. SW 400x.
(B) – Fragment of anundulating epithelium with sub-epithelial lymphoid-leukocyte exudateswhich are thinned by the intermediate parabasal layers and underlyingtissues. Cells are stained with hematoxylin and eosin. 100x.
(C) - Fragment of a flattened epithelium with parakeratosis and thinning. Hypersecretion of the terminal sections of mucinous cells of small salivary glands, striated duct (arrow), an abundance of myoepithelial cells are around the terminal sections of glands. Hematoxylin and eosin stain. SW 400x.

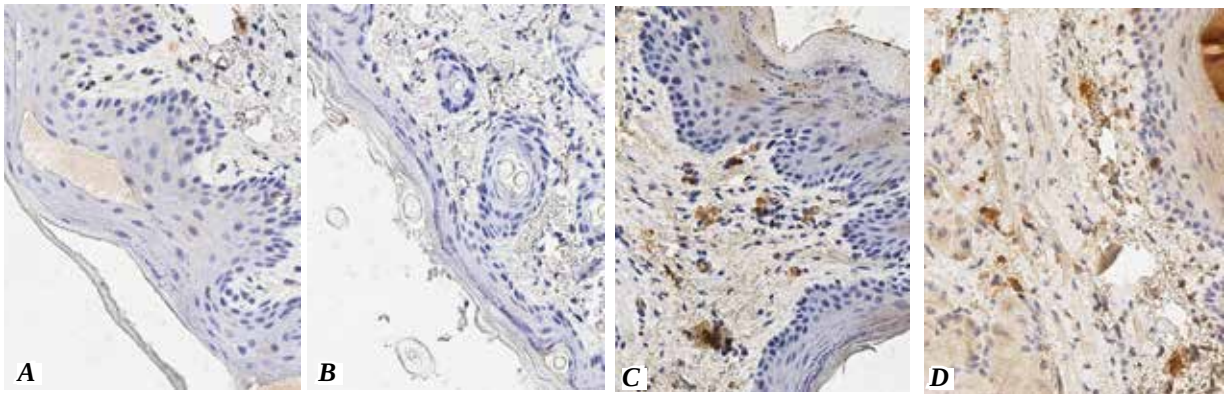

Figure 4. *Radiation and chemotherapy. Fragments of the cheek mucous membrane. IHV uv. 400x.*
(A) - negative reaction in the epithelium and weak in connective tissue with p53 protein.
(B) - negative reaction in the epithelium and in connective tissue with anti-apoptotic protein bcl-2.
(C) - marked decrease relative to the control of expression of the apoptotic marker CD-95.
(D) - Moderate intensity of reaction with a marker of CD 68 macrophages.

to the surface layers andthey moveinto the direction of keratinizing or non-keratinizing epithelium or it appears the phenomenon of parakeratosis.The intermediate cells are formed which are passing into surface cells.Surface cells are changing thetinctorial properties, they are characterized by the less expressedbasophilia or even cytoplasm eosinophilia.They are largesize and have polygonal shape.Their nucleustake the form of vesicular, the vacuoles appear there – it is the phenomena of karyolysis, karyopicnosis and karyorexis. If fragments of the nucleus are eliminated from the cytoplasm, the cell takes on the form of horny scales (Fig. 1C).

The keratinized epithelium compares the part of the area (Fig. 1C), especially along the contact line with the teeth and in areas of the greatest mechanical impact that is providing a great strength and chemical resistance, in comparison its thickness, as a rule, is less than non-keratinizing.The phenomenon of parakeratosis is also the norm when cells with pyknoticnuclei and other organelles appear in the surface layers of the epithelium, morphologically close to keratinizing.In the maxillary and mandibular zones of the cheeks mucous membrane there is a predominantly non-keratinizing epithelium but in the intermediate zone it is located keratinizing.

Such differentiation, histoarchitectonics and epithelium cell polarization, as well as its connection with the underlying tissue is organized by the basement membrane which is visible as a faintly colored strip.It covers the papillae of its own mucous membrane plate.According to the technique taking of the gum mucous membrane the submucosa is often fragmented and does not allow us to trace the course of collagen fibers and blood vessels which havea consistent and commensurate with the relief of epithelial scallops structure.In the submucosal cheek base, especially in the intermediate zone and reraly the salivary glands (more often these are the groups of the terminal sections of the mixed glands, mainly the mucous membranes), there are more of them in the posterior sections.At the same time, single and grouped sebaceous glands are quite common, which is the norm due to the small thickness of the cheek, especially in the intermediate zone along the jaw line and in the retro-molar zone.Some authors consider their presence in the mucosa as an element of morphogenetic potencies and embryonic heritage of these oral tissue areas [*Tkachenko P et al., 2016*]. In the connective tissue there are neutrophilic granulocytes, small lymphocytes, plasmocytes and macrophages. Noteworthy it is large quantity of these cells are in the subepithelial layers due to the abundant development of the vasculature with the epithelium feeding and cell migration.CD-68 + macrophages as antigen-presenting and inducing immune responses of the cells are in large numbers and it is normal (Fig. 2A).

The high mitotic activity epithelium of the cheek mucous membrane is accompanied by the natural intensive elimination of its cells by apoptosis.The physiological nature of this process is evidenced by the high intensity of the reaction with CD 95 markers (Fig. 2B) and low with apoptosis regulating protein p53 and anti-apoptotic protein bcl-2 (Fig. 2C, Fig. 2D).Also high reaction intensity was noted with the HIF 1 alpha hypoxia marker in the surface layers especially (Fig. 2E), it is associated with the diffuse type of epithelial nutrition through the pores of the basement membrane from the plexus of microvessels in the submucosa.

During the irradiation and chemotherapy there is the ulcerative and necrotic damage of the cheeks mucous membranes in the number of areas (Fig. 3A), more protected areas in the epithelial layers go under partial flattening, delamination and desquamation (Fig. 3B).Hypersecretion of the mucous terminal sections of the small salivary and sebaceous glands is characteristic (Fig. 3C, Fig. 4).In the control group, the finger-shaped papillae of their own mucous membrane plate are introduced into the epithelial layer by 1/4-1/6 of its thickness, it contributes to trophicity and increases the area of the basement membrane, which plays an important exchange and regulatory-coordinating role, and itcontributes the integrity preservation of the epithelium.Under the influence of aggressive therapy in the mucosa, there is a sharp smoothing of the outgrowths of the connective tissue of its own plate.

Immune histochemical method is an antigen-antibody reactionwhich is implemented in the tis-

sue. It is unlike other molecular signs are accompanying the indicated and described tissue damage in the group with the iatrogenic mucositis model which are characterized by a weak reaction of the pro-apoptotic protein p53 (Fig. 4 A) and the anti-apoptotic protein bcl-2 (Fig. 4 B) with a marked decrease in the expression of the CD-95 marker (Fig.4 C) and the absence of significant dynamics of the marker of CD 68 macrophages (Fig. 4 D).

Conclusion

Thus, during the immunomorphological investigation, it was established that as a result of irradiation, the cheek mucous membrane of rats is characterized by dystrophic processes due to increasing tissue hypoxia and the induction of FAS-dependent apoptosis, which will lead to a progression of alternative oxidative processes inevitably: erosion, ulceration and the spread of inflammatory infiltration with a tendency to chronicity.

After the investigation at the local level, we identified both reversible radiation reactions and more severe injuries [*Tkachenko P. et al., 2016; Yessayan L, 2017; Zima D et al., 2019*]. All of them can be detected on the 14th day of the experiment. We believe that it is possible to extrapolate the data to humans, taking into account the variability of damage development.Currently, risk factors for mucositis include genetic polymorphisms, which require studies that could not be traced in the population of linear animals.In humans it is relevant the identification of prognostic groups of patients for the development of severe forms of mucositis.

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CONTENTS

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