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HISTOLOGICAL AND HISTOCHEMICAL CHANGES IN THE BRONCHIAL TREE OF THE LUNGS OF WHITE LABORATORY RATS UNDER CONDITIONS OF CHRONIC ENDOGENOUS NEOPLASTIC INTOXICATION

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Histological changes in the bronchi of rats with colorectal cancer include both: direct lesions due to metastasis and side effects from chronic intoxication and inflammatory processes. Such changes can significantly impair lung function and require appropriate therapy to alleviate the condition. Microscopically, it was found that under conditions of experimental oncogenesis in the lungs of experimental animals significant destructive and degenerative changes in the walls of large, medium and small bronchi were found, characterized by alteration of the mucosal epithelium with its detachment into the lumen bronchi, proliferation of lymphocytes and their accumulation in the form of large conglomerates in the wall. Immune function disorders were characterized by hyperplasia of peribronchial lymphoid tissue throughout the bronchial wall, with thinning of the epithelium up to its destruction. There was a remodeling of components of the ground substance and fibers with a predominance of sulfated glycosaminoglycans and the formation of bronchial wall fibrosis.

Key words: lungs, bronchi, histological and histochemical changes, experimental carcinogenesis, endogenous intoxication.

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ГІСТОЛОГІЧНІ ТА ГІСТОХІМІЧНІ ЗМІНИ БРОНХІАЛЬНОГО ДЕРЕВА ЛЕГЕНЬ БІЛИХ ЩУРІВ ЗА УМОВ ХРОНІЧНОЇ ЕНДОГЕННОЇ НЕОПЛАСТИЧНОЇ ІНТОКСИКАЦІЇ

Гістологічні зміни в бронхах щурів при колоректальному раку включають як прямі ураження через метастазування, так і побічні ефекти від хронічної інтоксикації і запальних процесів. Такі зміни можуть істотно погіршувати функцію легень і вимагати відповідної терапії для полегшення стану. Мікроскопічно встановлено, що за умов експериментального онкогенезу в легенях дослідних тварин відбуваються значні деструктивно-дегенеративні зміни стінок великих, середніх та малих бронхів, що характеризувалося альтерацією епітелію слизової оболонки з відшаруванням його в просвіт бронхів, проліферацією лімфоцитів та скупченням їх у вигляді великих конгломератів у стінці. Напруження імунних функцій характеризується гіперплазією перибронхіальної лімфоїдної тканини по всій товщі стінки бронха, з витонченням епітелію аж до його руйнування. Відбувається ремоделювання компонентів основної речовини та волокон з превалюванням сульфатованих глікозаміногліканів і формуванням фіброзу стінки бронхів.

Ключові слова: легені, бронхи, гістологічні і гістохімічні зміни, експериментальний онкогенез, ендогенна інтоксикація.

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Chronic endogenous neoplastic intoxication develops as a result of the progression of malignant tumors and is accompanied by the accumulation of toxic tumor metabolic products in the body [2]. This process can cause changes in many organs and systems, including the lungs [11]. Histological changes in the bronchi of rats with colorectal cancer include both: direct lesions due to metastasis and side effects from chronic intoxication and inflammatory processes. Such changes can significantly impair lung function and require appropriate therapy to alleviate the condition [8]. Due to generalized intoxication, toxins released by tumor cells cause tissue hypoxia and oxidative stress, and protein, fat, and carbohydrate metabolism is disrupted. Chronic inflammation caused by the immune response leads to tissue remodeling and fibrosis [3].

Today, colorectal cancer is the fourth most deadly cancer in the world, killing nearly 900,000 people annually. The incidence varies greatly around the world and is closely related to elements of the so-called Western lifestyle [6, 9]. The incidence is higher in men than in women and increases sharply with age; the average age at diagnosis in developed countries is about 70 years old. Despite strong hereditary components, most cases of colorectal cancer are sporadic and develop slowly over several years through the adenoma-carcinoma sequence [7, 12, 13].

The purpose of the study was to investigate morphological changes in the structural components of the bronchi of the white rat lungs in N,N-dimethylhydrazine-induced colon adenocarcinoma.

Materials and methods. The experiment was modeled on 85 outbred white male rats weighing 190±5 g. The experimental animals were kept in standard vivarium conditions, on an ad libitum basic diet. All animal manipulations were performed in accordance with the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986) [10].

The experimental animals were divided into 2 groups: Group I – 15 control animals, Group II – 70 animals with induced colorectal adenocarcinoma in situ. To model colorectal adenocarcinoma, N,N-dimethylhydrazine hydrochloride (Sigma-Aldrich Chemie, Japan, series D161802) was used, which was dissolved in isotonic sodium chloride solution. The carcinogen was injected subcutaneously into the interlobular region at a dose of 7.2 mg/kg body weight (regarding active ingredient) once a week for 30 weeks. Adenocarcinoma of the colon in situ was histologically confirmed in all experimental animals of group II after 30 weeks of carcinogen administration.

The material for histological studies was collected according to the standard method [1]. Lung tissue fragments were fixed in a 10 % buffered formalin solution, after which they were processed in an automated tissue processor LOGOS One. Tissues were paraffin-embedded and histological blocks were formed using a TEC2800 embedding station, and further sectioning was performed using an AMR-400 rotary microtome. The histological specimens were stained with hematoxylin and eosin, Periodic Acid Schiff reaction (PAS), Hale staining method, silver impregnation by the Gordon-Swets method, examined using a MICROmed SEO SCAN light-optical microscope, and a Vision CCD Camera was used for photographic documentation.

Results of the study and their discussion. Microscopic examination of the lungs of the intact group white rats showed that the bronchi of the large, medium and small bronchi had a typical wall structure and included three tunics: mucosa with a submucosal layer, fibrocartilaginous and adventitia. The mucosa contained an epithelial layer, which was formed by a simple pseudostratified ciliated epithelium, a thin lamina propria, which was represented by a thin layer of loose connective tissue and muscularis mucosa. The submucosa was formed by loose connective tissue with fibroblastic cells and a connective tissue stroma with well-defined collagen, reticular fibers and poorly developed elastic fibers. The muscularis mucosa was formed by smooth myocytes, appeared in large bronchi and was very well developed in small bronchi. The adventitia was formed by well-developed loose connective tissue with pronounced, argyrophilic collagen and reticular fibers, poorly developed elastic fibers and ground substance. Histologically, it was found that a species-specific feature of the bronchi of the white rats lungs was the absence of cartilaginous islets in the medium-sized bronchi (Fig. 1).

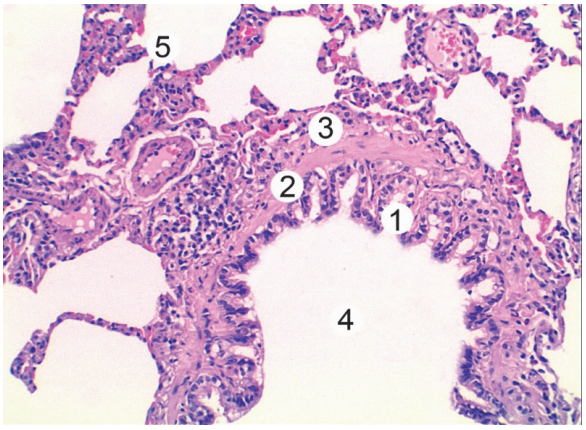
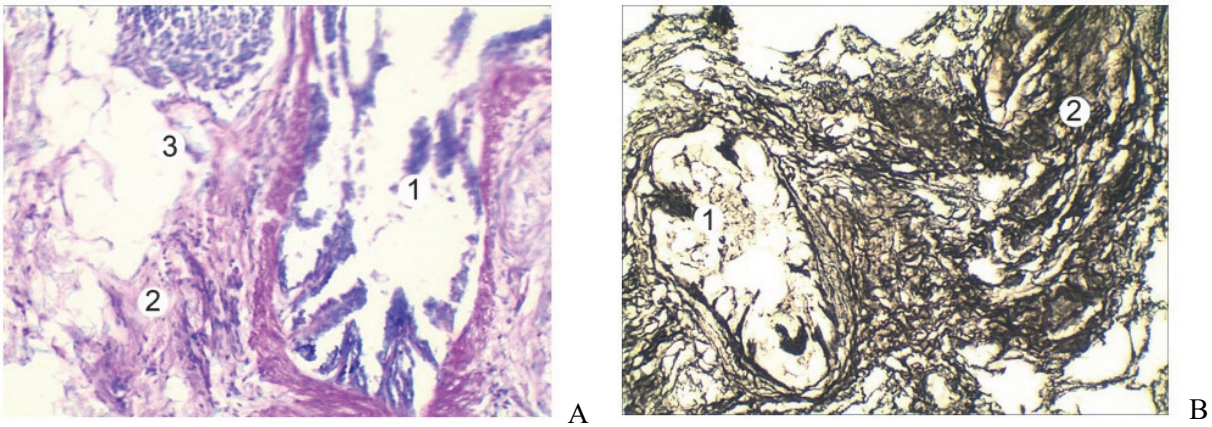


Fig. 1. Microscopic condition of the medium-sized bronchus in the intact rat lung. Mucosa (1), muscularis mucosa (2), adventitia (3), bronchial lumen (4), respiratory portion (5). Hematoxylin and eosin staining. x 100.

Microscopic examination of the bronchi of the lungs of the second experimental group of animals with modeled carcinogenesis showed significant remodeling of the bronchial walls of all calibers, which was manifested by deformation of their walls with significant expansion of the lumens, mainly of large and medium-sized bronchi or sharply narrowed with obstruction of the lumens both due to the shortening of muscularis mucosa smooth myocytes and serous-mucous content. There were necrotic and erosive changes in the mucosal epithelium with its desquamation into the lumen and the formation of mucocellular detritus. The epithelial cells were destructured, necrotic, contained hyperchromatic nuclei, intercellular junctions were disturbed, cell detachment with exposure of the basement membrane was determined (Fig. 2A).

The reorganization of the mucosa and adventitia connective tissue was characterized by hypertrophy of reticular and collagen fibers, degradation of glycoproteins and glycosaminoglycans of the connective tissue ground substance, with their redistribution and predominance of sulfated glycosaminoglycans. The fibers in the wall were argyrophilic when impregnated with silver salts, grow with the formation of bronchial and peribronchial fibrosis, were unevenly thickened, swollen, form thick bundles that stick together, or were unevenly thickened, loosened and fragmented (Fig. 2B).

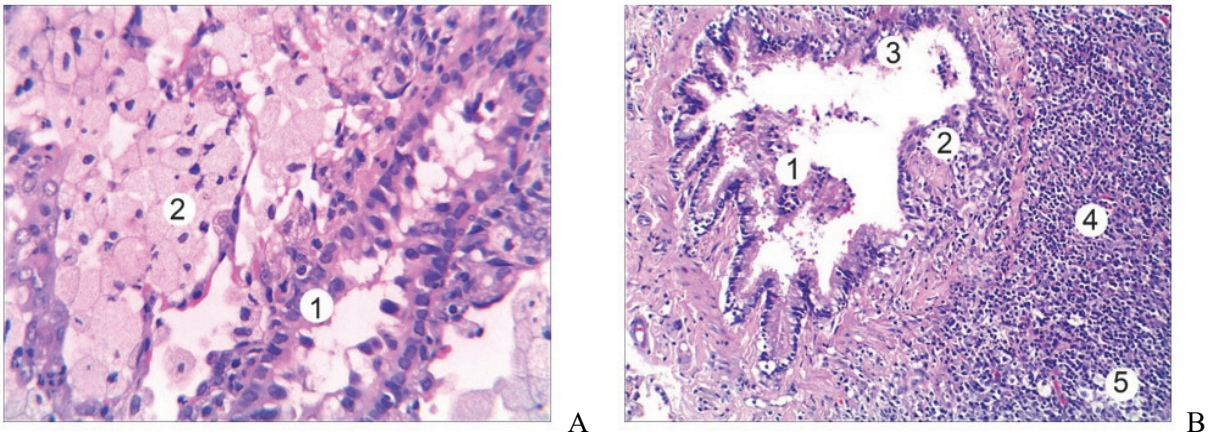


A B

Fig. 2. Histochemical changes in the lung of white rat under conditions of modeled carcinogenesis. A – Desquamation of the epithelium into the bronchial lumen (1), collagen fibrils of peribronchial connective tissue with mildly expressed PAS reaction-positive properties (2), pronounced "Hale" positive properties of glycosaminoglycans (3). Staining by the Mowry method. x 200. B – Homogeneous, argyrophilic fibers of mucosal folds (1), thick growths of collagen fibers of adventitia into the lung parenchyma (2). Gordon and Sweet's staining method. x 200.

Under the conditions of experimental carcinogenesis, numerous foamy macrophages were detected in the lung perenchyme, peribronchial and bronchial wall, with a characteristic feature of numerous lipid inclusions in the cytoplasm as a protective reaction to the modeled pathological process (Fig. 3A).

The stress of immune functions on the modeled pathological process was characterized by hyperplasia of peribronchial lymphoid tissue throughout the bronchial wall, with thinning of the epithelium up to its destruction (Fig. 3B).



A B

Fig. 3. Microscopic changes in the lung of white rat under conditions of modeled carcinogenesis. A – Terminal bronchiolar wall (1) foamy macrophages (2). Hematoxylin and eosin staining. x 400. B – Mucocellular detritus in the bronchial lumen (1), wall deformation (2), epithelial destruction (3), proliferation of peribronchial lymphoid tissue (4), foamy macrophages (5). Hematoxylin and eosin staining. x 200.

The formation of volumetric inflammatory lymphoid infiltrates in the lungs of white rats was also studied by scientists [14], who showed a dynamic increase in lymphoid infiltration of the lungs under the influence of sodium glutamate, sodium nitrite, and Ponso4R, which reflects the reaction of elements of the local protective barrier, to the action of the components of the complex, which primarily act as antigens, which is reflected in the activation of the processes of antigen-dependent differentiation of lymphoid cells and occurs in a typical induced immune defense response to pathological exogenous exposure.

Idiopathic pulmonary fibrosis remains an urgent task for researchers, scientists, clinicians, and pulmonologists. Our results of microscopic examination of the white rats lungs after modeling carcinogenesis and detection of fibrotic changes in the organ were consistent with scientific data [4, 5], which presented the results of experimental modeling of lung fibrosis in rats in the remote period of modeling this injury.

Conclusion

The modeled colon carcinogenesis led to a significant remodeling of the bronchial tree of the lungs of experimental animals, which was histologically confirmed by alternative wall changes with epithelial desquamation and the formation of mucocellular detritus, hyperplasia of peribronchial lymphoid tissue, the

presence of foamy macrophages, degradation of the amorphous component, proliferation of peribronchial connective tissue fibers with the development of peribronchial fibrosis.

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