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Morphofunctional Characteristics Of The Oral Mucosa Of Experimental Rats In Experimental Carcinogenesis

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ABSTRACT: Diseases of the gastrointestinal tract are often accompanied by changes in the oral cavity. This is largely due to morphological and functional unity of the mucous membrane of the mouth and entire digestive tract. According to numerous publications in recent years, at the end of the XX-beginning of the XXI century, there is a significant increase in the number of people suffering from cancer of the colon and rectum. This localization accounts for 15% of all initially diagnosed tumors of all localizations (30% of them are represented by rectal cancer).

Key words: carcinogens, hydrazines, afta, oncology, ulcer, hyperkeratosis, atrophy, acanthosis, hyperplasia, parakeratosis, dysplasia, adenocarcinoma, infiltration.

1. INTRODUCTION.

Carcinogenesis is a multi-factorial and multi-stage process, including a chain of genetic and non-genetic damage to the cell, reversible in the early stages and progressing only in people at risk[1,6].

Carcinogenesis is the result of human exposure to exogenous and endogenous factors. The first include environmental factors and lifestyle, the second-the genetic, immunological and hormonal properties of the body. It is known that carcinogenesis is a multi-stage process in which two major stages are distinguished-initiation and promotion. At the initiation stage, the chemical carcinogens entering the body undergo a biological transformation, including metabolic activation and deactivation. The active metabolites of the carcinogens interact with the DNK of the target cells to form adducts. If complete DNK repair does not occur, the genotoxic effect of carcinogens leads to mutations and activation of oncogenes with the

appearance of"initiated cells". The subsequent stage of tumor promotion involves the selection and proliferation of initiated cells with further accumulation of mutations, neoplastic transformation, and tumor formation[2,3].

About 100,000 people die from colorectal cancer every year [4]. The highest mortality is recorded in the Czech Republic, Hungary (34.3 per 100,000 people) and New Zealand (26.4), the lowest-in the United States (15.2), Israel (17.9), the Netherlands (17.7) and Bulgaria (17.2). The five-year survival rate in Europe ranges from 50% (in Switzerland, Finland, the Netherlands, Spain) to 30-39% (in Italy, Denmark, Great Britain, Germany and France)[9].

The life expectancy of patients with colon cancer is directly related to the degree of prevalence of the tumor process. When the disease is detected in the early stages (stage I), the five-year survival rate is quite high and is 93.2%, but with the growth and metastasis of the tumor, a sharp decrease in this indicator is observed. Thus, when diagnosing the process at stage II, the five-year survival rate decreases to 72.2% and is only 44.3% when regional lymph nodes are involved in the pathological process (stage III). In the presence of distant metastases (stage IV), the five-year survival rate does not exceed 8,1% [4,5].

Artificially induced tumors with the help of certain carcinogens in laboratory animals provide an opportunity to study various aspects of carcinogenesis that cannot be effectively studied directly on the human body[7,10,13]. To date, a significant number of experimental models of the initiation of tumor growth in various organs have been developed. One of them is the dimethylhydrazine model [8]. The metabolic changes that occur during the induction of the tumor process with the help of DMH are close to those that occur in humans with the development of colon cancer [8].

Morphological analysis of tumors in experimental animals showed that in animals of all experimental groups, neoplasms characteristic of the carcinogenic effect of DMH were registered (intestinal adenocarcinomas, hemangioendotheliomas, tumors of the skin and its appendages localized in the anal region, as well as leukemias). The intake of VSH into the animals ' bodies practically did not change the morphological picture of tumors.

The aim of the study was a comprehensive, morphological study of tissues of the oral cavity in rats in experimental carcinogenesis.

2. MATERIAL AND METHODS.

The study was performed on 168 sexually mature mongrel white male rats with a body weight (175.0±4.2) g, which were kept in standard vivarium conditions. All manipulations with experimental animals were carried out in compliance with the rules of the "European Convention for the Protection of Vertebrates Used for Research and Other Scientific Purposes", as well as according to the "Scientific and Practical recommendations for the maintenance of laboratory animals and work with them"[11].

The animals were placed on a hardwood mat in cages made of polycarbonate shoe boxes (two to three per cage) in a windowless room that was lit for 12 hours each day and maintained at a temperature of 22±1 °C and a relative humidity range of 30% to 70%. Throughout the studies, the rats were allowed free access to the laboratory diet and drinking water (provided in bottled water). All food cups and water bottles were changed at least twice a week.

The experimental animals were divided into the following groups: the control group of animals – 84 individuals; the experimental group of animals with simulated adenocarcinomatosis of the colon – 84 individuals. Every 30 days of the experiment, 12 animals were removed from the control and experimental groups.

Carcinogenesis was modeled by administration of 1,2-dimethylhydrazine dihydrochloride (DMH) (Sigma-aldrich chemie, Japan), previously diluted with isotonic sodium chloride solution. The carcinogen was injected subcutaneously into the interscapular area at a dose of 7.2 mg / kg once a week for 30 weeks, clearly by the weight of the animal at the rate of 0.1 ml of DMH solution per 10 grams of body weight.

Histological examination was performed with a Leika binocular microscope (Germany), magnification of the lens 10x, 40x, photo documentation was performed with a color web camera MD130.

3. THE RESULTS OF THE STUDY.

The most common DMH-induced colon tumors were macroscopically divided into exophytic (up to 80%) and exophytic-endophytic (5-10%) neoplasms. Histological studies have shown that the induced intestinal tumors were represented by tumor formations of 2 types: benign polyps (striated and adenomatous) and malignant exophytic adenocarcinomas, which, in all probability, are the result of malignancy of adenomatous polyps.

The adenomatous tissue of the polyps was well separated from the mucosa forming the base of such a tumor, and there were no signs of invasion. Exophytic adenocarcinomas were characterized by larger sizes compared to the size of polyps; in addition, they were characterized by pronounced signs of cellular and structural atypia of the parenchyma. A mandatory characteristic component of their structure was the presence of irregular tubular formations.

The base of such tumors, as a rule, was represented by atypical glandular tissue with small irregularly shaped glands that showed signs of invasive growth in the underlying deeper parts of the colon wall.

Histological examination revealed that after 1 month from the beginning of the experiment, morphological changes in the tissue with uneven atrophy, smoothing of the epithelial papillae and hyperchromia of the basal layer cells were detected in the oral mucosa of the experimental animals. Under the epithelium in the cellular-fibrous stroma, single blood vessels are identified, as well as layers of cartilage tissue in the main substance of which single mature chondrocytes are visible. (Figure 1).

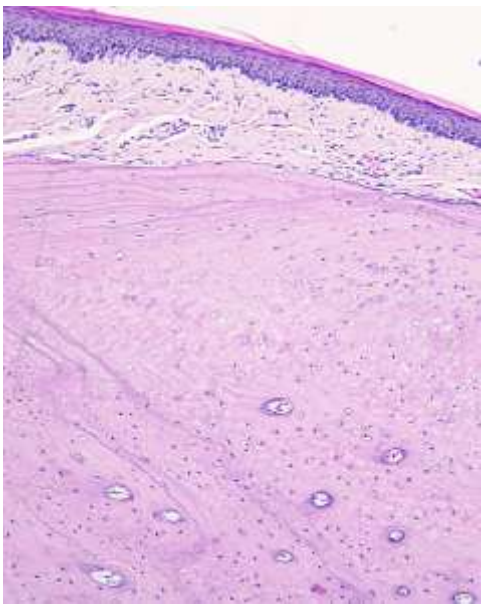

Figure 1. Flat epithelium with uneven atrophy, smoothing of the epithelial papillae, the cells of the basal layer are hyperchromic. Layers of cartilage tissue in the main substance, which determines the single mature chondrocytes. 1 month. Stained with hematoxylin and eosin, magnification about 06x20.

Microscopic studies of the oral mucosa of animals 2 months after the start of the administration of DMH showed that in the fragments of the oral mucosa, among the cells of the squamous epithelium, dark-colored glandular structures, as well as a cartilaginous plate, are determined. Under the layers of cartilage tissue, you can see a cellular-fibrous stroma with a large number of polygonal and elongated cells with hyperchromic nuclei (Fig. 2,3).

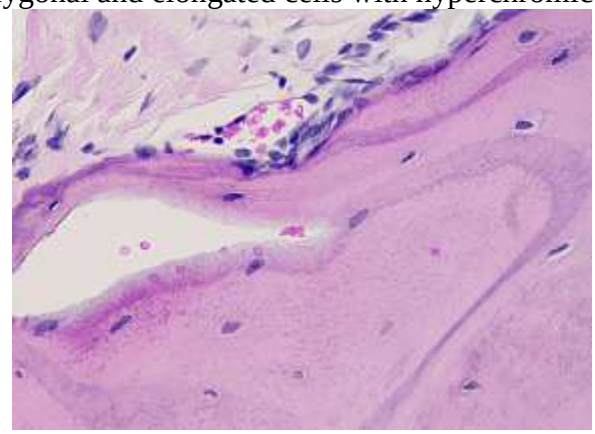

Figure 2. A fragment from the oral mucosa, among the cells of the squamous epithelium, dark-colored glandular structures and a cartilaginous plate are determined. 2 months Staining with hematoxylin and eosin, increase of about 03x40

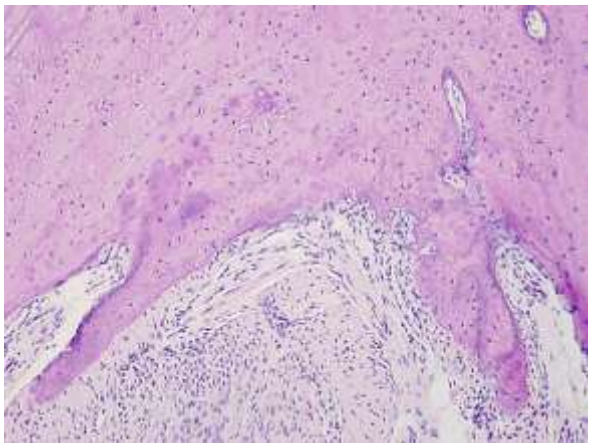

Figure 3. Under the layers of cartilage tissue, a cellular fibrous stroma with a large number of polygonal and elongated cells with hyperchromic nuclei.2 months of staining with hematoxylin and eosin, an increase of about 07x20.

The formation of chronic neoplastic intoxication (3 and 4 months) under the action of DMH leads to the reorganization of chondroitin-like cells: an accumulation of polymorphic atypical chondroid-like cells with signs of nuclear polymorphism (Fig.4) and among the hyaline fibers and connective tissue, a focal accumulation of histiogenic cells and angiomatosis (Fig. 5).

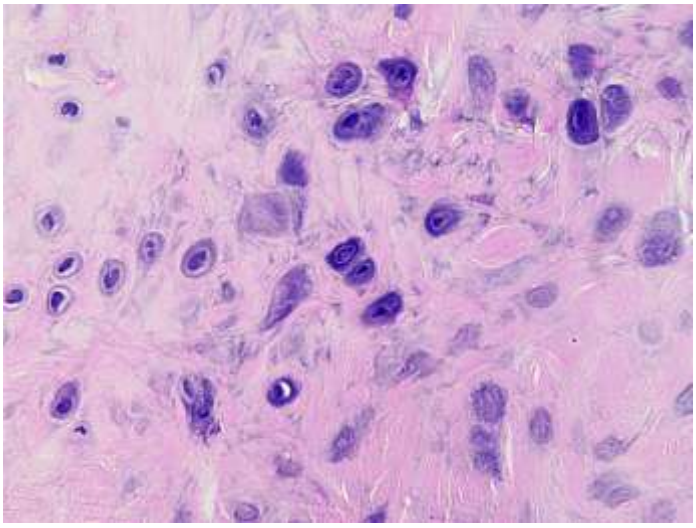

Figure 4. In the field of view, a cluster of polymorphic atypical cells with signs of nuclear polymorphism. 3 months Staining with hematoxylin and eosin, magnification about 12x40.

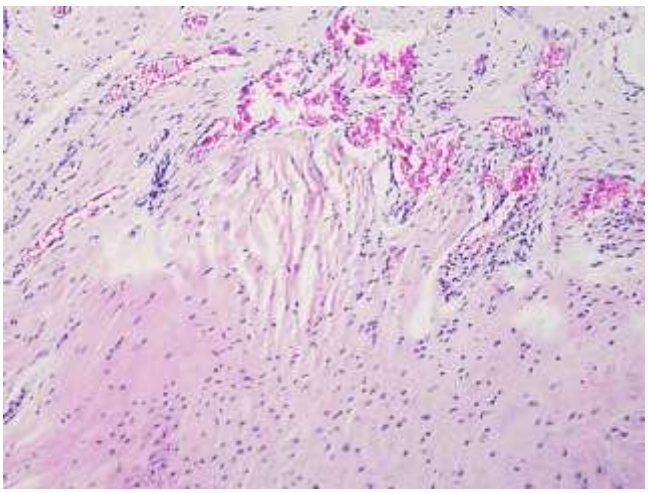

Figure 5. Among the hyaline fibers and connective tissue, there is a focal accumulation of histiogenic cells and angiomatosis. 4 months Stained with hematoxylin and eosin. The magnification is about 8x10.

Histological studies at 5 and 6 months after the start of DMH administration revealed significant destructive changes in the tissues of the oral mucosa. A fragment of a cartilaginous plate with areas of homogenization, necrotic changes in the studied tissue samples contain paretically expanded blood vessels, single polymorphic tumor cells are determined (Fig. 6).

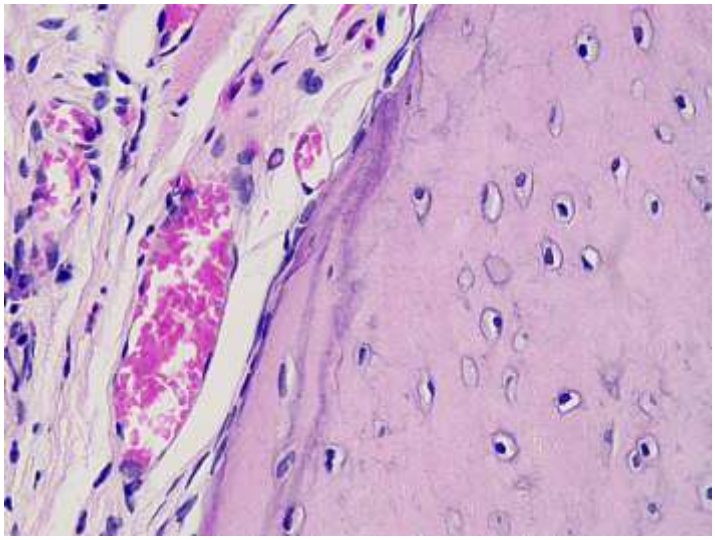

Figure 6. Blood vessels are paretically dilated, single polymorphic tumor cells are detected - 6 months. Stained with hematoxylin and eosin, magnification about 95x40.

Histological studies of the oral mucosa of animals 7 months after the DMH lesion revealed deep destructive-degenerative changes in all components of the organ. Among the fragments of hyaline-fibrous cartilage tissue, there is an accumulation of bone marrow fibroreticular cells with an admixture of fat cells, as well as tumor cells (Fig.7).

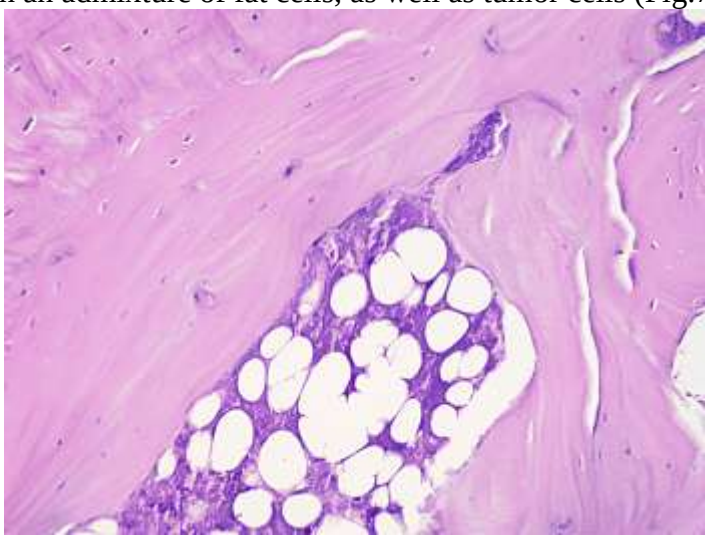

Figure 7. Among the fragments of hyaline-fibrous cartilage tissue, there is an accumulation of bone marrow fibroreticular cells with an admixture of fat cells, as well as tumor cells.7 months. Stained with hematoxylin and eosin, magnification about 14x20.

During this period of experience, the tissues of the oral mucosa are characterized by the presence of bone marrow in the layers of cartilage tissue, which leads to thickening of the stromal connective tissue and fibrosis (Fig. 8).

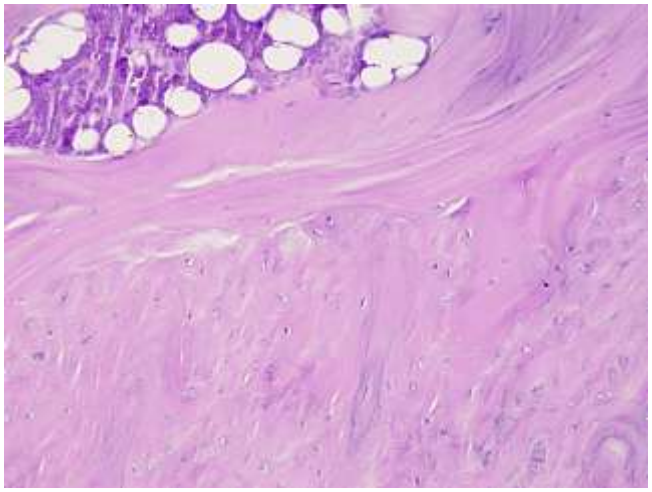

Fig. 8. Elements of bone marrow in the layers of cartilage tissue.7 months Staining with hematoxylin and eosin, increase of about 09x20.

4. CONCLUSION.

Thus, the histological studies of the oral mucosa of animals in the dynamics of the formation of chronic neoplastic intoxication induced by the administration of dimethylhydrazine established the development of destructive-degenerative and sclerotic changes in the oral mucosa, the severity of which increased accordingly to the period of observation.

As a result of the study of the oral mucosa and surrounding tissues in experimental intestinal carcinogenesis in rats, the following changes were detected; in the first 2 months, no changes characteristic of a tumor lesion were observed. At 3 months, there were clear signs of polymorphism of the nuclei of atypical polymorphic cells. At the 4th and 6th months, angiomatosis of the mucosa and surrounding tissues with paretic expansion of their lumen was noted. At the 7th month of experimental carcinogenesis in the oral mucosa, signs of metastasis of tumor cells with bone marrow elements in the adjacent tissues were noted, which indicates a high risk of the action of carcinogenic substances, in particular, the introduction of 1,2-dimethylhydrazine dihydrochloride (DMH), not only on the intestine, but also on the entire gastrointestinal tract, including the oral mucosa and surrounding tissues.

Conclusion. The above-mentioned changes in the colon and oral mucosa caused by a simulated chemical carcinogen indicate a high risk of developing a malignant tumor with spread to all parts of the gastrointestinal tract, including the oral mucosa. The obtained results of experimental scientific work are a prerequisite for the development of preventive measures aimed at reducing the risk of spreading the neoplastic process to the oral mucosa and the need to develop an algorithm for providing dental care.

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