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MORPHOLOGICAL STRUCTURES OF THE COLON IN RATS DURING CHEMOTHERAPY FOR BREAST CANCER.

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ABSTRACT

Introduction: The prevalence of carcinogenic substances globally has led to an increase in malignant neoplasms. Chemotherapy, particularly using paclitaxel, is a modern, high-tech approach to treating malignancies by disrupting cell division and metabolism. Understanding the effects of paclitaxel on mammary cancer and associated pathological changes in rats is crucial for improving therapeutic outcomes.

Methods: The study involved 52 white outbred female rats aged six months, divided into control (n=40) and experimental (n=12) groups. Mammary cancer was induced using 7,12-dimethylbenzanthracene, and paclitaxel was administered intravenously at a dose of 0.2 mg/kg to the experimental group. The rats' behavior, physiological state, and various histological parameters of the colon were monitored and analyzed.

Results: Chemotherapy with paclitaxel in rats resulted in a 5.94% decrease in body weight compared to the control group. The colon length in the experimental group was 17.84% shorter. Morphological examination revealed significant inflammation, a decrease in goblet cells, and increased numbers of lymphocytes, macrophages, and mast cells in the colon mucosa. These changes indicate severe epithelial damage, collagen fiber thickening, and chronic inflammation, leading to mechanical damage and microbleeding in the colon tissue.

Conclusion: Paclitaxel-induced chemotherapy in rats causes notable atrophic and inflammatory reactions in the colon, decreasing its functional activity. This research underscores the importance of understanding chemotherapy's side effects to mitigate gastrointestinal damage and improve cancer treatment protocols.

KEYWORDS: Oncology, chemotherapy, epithelium, malignant tumor, inhibitor, mitosis, crypt, saccular cells, columnar cells, mast cells, neutrophil, lymphocyte, macrophage and plasma cell.

INTRODUCTION

The number of types and effects of carcinogenic substances is increasing in the world. This causes an increase in malignant neoplasms among the population. In oncology, chemotherapy is a high-tech modern method of combating malignant tumors by introducing chemical agents into the human body. Chemotherapy drugs affect tumor cells in different ways.

Paclitaxel is a chemotherapeutic drug of plant origin, a mitosis inhibitor, used to treat malignant tumors. They block cell division, disrupt the function of cell microtubules and some enzyme proteins. They change the metabolism of amino acids, nucleic acids, fat synthesis and affect cellular respiration.

This drug has been widely used for chemotherapy since the 90s of the last century. Paclitaxel was first isolated from the Pacific yew (Taxus baccata) in the 1960s. Today, mitosis inhibitors are widely used to treat breast cancer.

The object of the study was 52 white outbred female rats aged 6 months in a vivarium.

MATERIAL AND METHODS

The experiments were carried out in a vivarium on 52 white outbred female rats. It involved 6-month-old rats. The experiments complied with the ethical rules for the use of animals and the requirements of the Helsinki Congress. Before the start of the experiments, all mature rats were quarantined for a week, and after eliminating somatic or infectious diseases, they were transferred to a vivarium under the same conditions. During the experiment, the behavior and physiological state of animals in the standard and experimental groups were monitored. The rats were divided into 2 groups (n = 52): control group 1 (n = 40); 2 (n = 12) - groups of experimental animals from 6 months of age. To induce breast cancer in experimental groups, breast cancer was induced in rats with the carcinogenic agent 7,12-dimethylbenzanthracene. A success rate of 68.9% was achieved, meaning 48 rats were induced with a carcinogen. 7,12-dimethylbenzanthracene at a dose of 0.1 mg subcutaneously into the mammary gland of 16 female rats. Rats of group 2 (n = 12) were administered paclitaxel intravenously at a dose of 0.2 mg/kg

A total of 52 rats were used in the experiments, only 1 of them died during the experiments, which caused mammary cancer in the experimental animals.

RESULTS

When we modeled mammary cancer in 6-month-old rats and administered chemotherapy with paclitaxel, we encountered various pathological changes.

The body weight of 6-month-old rats with breast cancer treated with paclitaxel ranges from 217.23 g to 259.34 g, with an average of 223.72 ± 2.37 g, which is 5.94% less than that of the control group experience (Fig. 1).

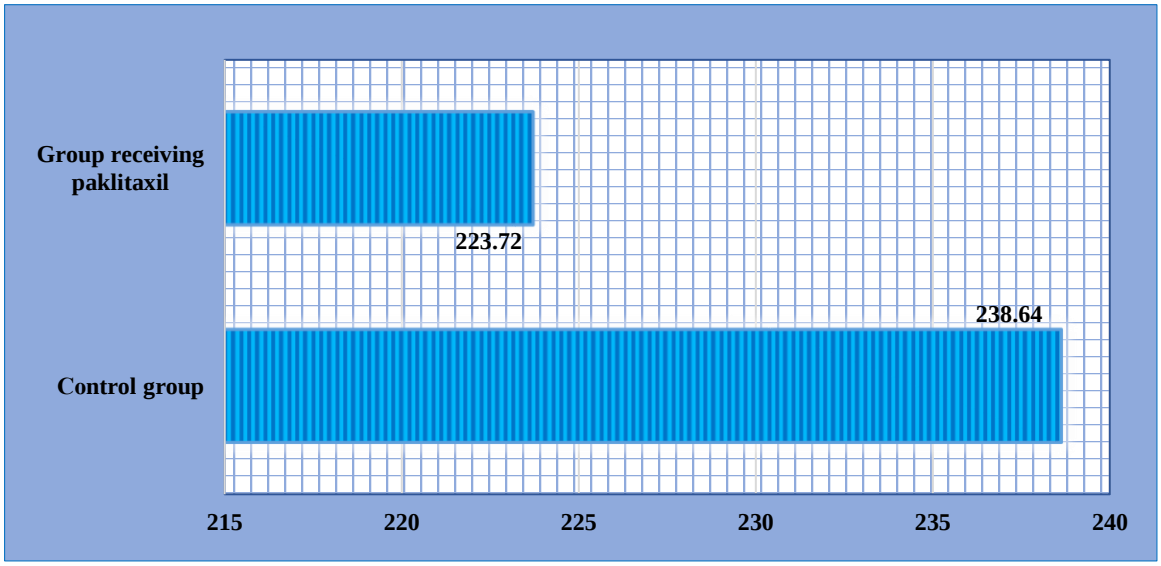

Figure 1. Change in body weight of rats in the experiment (g).

Visual assessment did not reveal differences between the intestines of the group of rats with breast cancer after chemotherapy with paclitaxel and the rats of the control group of the experiment, however, the organometric parameters of the colon remained significantly lower than the values. The length of the colon of rats ranges from 11.09 cm to 13.07 cm, with an average of 12.02 ± 0.3 cm, which showed that it is 17.84% shorter than that of the control group.

A morphological study of the colon of rats in the control and experimental groups was carried out in preparations stained with hematoxylin and eosin. The relative numbers of neutrophils, lymphocytes, plasma cells, fibrocytes and fibroblasts per 1000 cells were determined at 400× magnification.

The experiment noted changes in the nature of acute inflammation that developed during chemotherapy for breast cancer, and the phenomenon of restoration of the architectonics of the colon mucosa. The number of goblet cells is reduced, the cellular composition is represented mainly by lymphocytes, plasma cells, macrophages and single neutrophils. There was a sharp increase in the number of mast cells, most of which are in degranulated form, compared to the control group of experimental animals. The data obtained suggest that the structures of the large intestine of experimental animals are damaged under the influence of chemotherapy and this is consistent with the data of modern literature on the inflammatory effect of chemotherapy on the intestine. The formation of chronic inflammation in the colon of rats occurred against the background of the development of inflammatory and traumatic morphological changes in its wall.

In morphological studies, the distal colon of rats in the control and experimental groups was covered with intact and bordered columnar epithelium.

The crypts were thin and deep, the crypts ranged from 138.64 μm to 174.21 μm, with an average of 156.12±14.06 μm, which was 10.02% less deep than the control group.

Their epithelial lamina includes round and oval goblet cells. In the epithelium of the crypt bottom there are from 2 to 4 cells that divide by mitosis. Cellular elements, such as fibroblasts, fibrocytes, lymphocytes, single neutrophils, histocytes and loose fibrous connective tissue, are diffusely distributed among the crypts located in the stroma of the mucosal plate. The basal surface of the private lamina of the mucous membrane is represented by loose fibrous connective tissue, as well as cellular elements such as fibroblasts, fibrocytes and, in small quantities, lymphocytes

and macrophages. The internal spaces of the lymphatic vessels are not dilated.

The mucous membrane of the colon consists of 3-5 layers of smooth muscle cells with granular cytoplasm on the basal surface of the muscular plate. The submucosa contains loose fibrous connective tissue consisting of cellular elements and microvascular vessels, including several fibroblasts and fibrocytes, lymphocytes and histiocytes. The accumulation of lymphocytes is observed in individual lymphatic vessels. The transverse and longitudinal smooth muscle layers are also represented by smooth muscle cells with granular cytoplasm. The serous layer consists of loose fibrous connective tissue and one layer of flattened mesothelial cells.

In contrast to the control group, in rats receiving chemotherapy for breast cancer, during a morphological study, goblet cells were smaller, and the number of cellular elements increased in the lamina propria of the mucous membrane.

According to the analysis of our morphometric experiments, in rats receiving chemotherapy for breast cancer in the lamina propria of the colon mucosa, there was a significant increase in the number of cellular elements in the connective tissue between the crypts and the surface of the basement membrane by 29 - 34%, respectively, compared with the control group. Compared with the control group, the number of lymphocytes among the cellular elements in rats receiving chemotherapy for breast cancer in the experiment ranged from 30.27 to 37.41, on average 33.92±1.08, which is 58.5% more. than in the control group. In this experiment, the number of neutrophils ranged from 1.85 to 1.36, on average 2.15±0.5, which indicated that it was 57.7% more than in the control group of the experiment.

The number of plasma cells in the compared groups did not differ significantly. The number of macrophages in rats receiving chemotherapy for breast cancer increased from 5.39 to 8.83, an average of 7.11±0.68, which is 2 times more than in the control group of the experiment.

The number of oval and round goblet cells in rats with breast cancer treated with chemotherapy ranges from 58.14 to 64.59, with an average of 61.27±9.07, which is 7.93% less than in the control group of the experiment, the number of columnar cells ranges from 16.24. to 21.63, with an average of 18.98±3.1, which is 58.18% less than that of the control group of experience.

The number of degranulated mast cells ranges from 10.25 to 15.49, with an average of 12.92±0.3, which is 39.86% more compared to the control group.

From micrographs of histological sections of the colon, the absolute number of cellular elements lying in the lamina propria of the mucous membrane was determined by counting on a standard area (1000 μm^2). The number of goblet cells in the crypt was counted. The relative volume density of the stained material in the lamina propria was determined in a standard unit of epithelial area (1000 μm^2).

At the end of the experiment, the depth of the crypts of the colon mucosa in animals receiving chemotherapy was less than in the control group. This indicates the negative effect of chemotherapy.

Colon material obtained from animals receiving chemotherapy was characterized by degenerative and atrophic conditions. The appearance of goblet cells is darkened, expanded, and unevenly covers the mucous membrane. Round cell infiltration is observed polylocally in the submucosa.

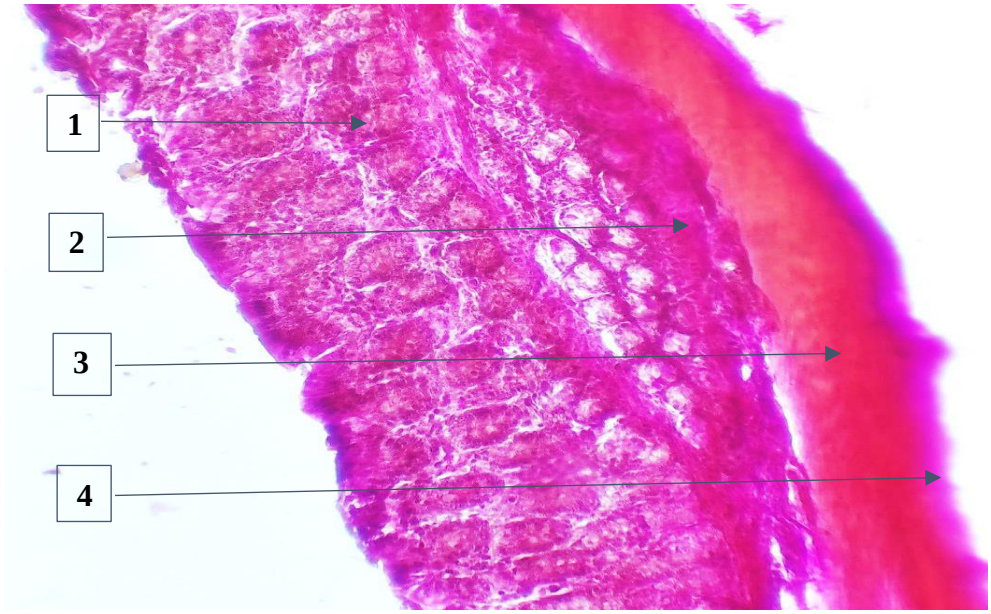

Figure 2. Microscopy of the colon wall during chemotherapy for breast cancer in experimental rats. Hematoxylin-eosin staining. OK 10 x OB 400. 1-mucous membrane, 2-submucous membrane, 3-muscular membrane, 4-serous membrane.

In samples of the mucous membrane of the large intestine of animals from the group receiving chemotherapy, swelling and pathological changes in the submucosal layer of the epithelium are observed compared to the control group. In the submucosa of the colon, thickening of collagen fibers and an increase in connective tissue were observed. In this case, damage to all tissues of the large intestine led to an increase in the thickness of the entire intestinal wall (Fig. 2).

Compared with the control group, in rats receiving chemotherapy for breast cancer, a statistically significant increase in the relative volume fraction of collagen fibers in the lamina propria of the mucous membrane between the crypts and an increase in the volume fraction in the basal surfaces were observed in the experiment. There was also a trend toward an increase in the relative volume fraction of fibers on the basal surface of the lamina propria. The volume fraction of collagen fibers in the lamina privatum of the mucous membrane was different in the compared groups. In the crypts, the ratio of the relative volume fraction of collagen fibers to mature collagen fibers changed.

CONCLUSION

In the colon, reactive morphological changes develop in the epithelial layer, characterized by a decrease in the volume fraction of the contents of goblet cells. This also causes a tendency for the number of goblet cells in each crypt to decrease. In the lamina propria of the mucous membrane, the number of cellular elements and the relative content of lymphocytes, neutrophils and macrophages among them increases. In an experiment, the use of chemotherapy for breast cancer in rats changes the ratio of formed and unformed collagen fibers in the crypts of the colon mucosa in the distal intestinal wall compared to the control group. Foci with erosive changes were noted separately.

Colon mucosal samples from animals in the chemotherapy group contained more mast cells than those in the control group. They were mainly found in the lower third of the descending colon and its connective tissue. In other words, mast cells were predominantly localized in the colon tissue perivascularly and were at different stages of functional activity. It

is characterized by an increase in cellular composition, that is, an increase in macrophages and plasma cells, as well as an increase in the number of lymphocytes. Their number increased by 26.8 and 27.1%, respectively. Significant differences were found in mast cells, the number of which increased by 39.86% in samples of the colon mucosa of animals treated with chemotherapy compared to the control group.

The number of goblet cells decreased by 7.99%. Significant granular heterogeneity was observed in their cytoplasm.

Based on the data obtained, we can conclude that signs of atrophy and inflammatory reaction in the colon led to a decrease in its functional activity. This causes mechanical damage to the colon mucosa under the influence of feces and causes various types of macro- and microbleeding.

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