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MICROSCOPIC CHANGES IN THE VESSELS OF THE HEMOMICROCIRCULATORY BED OF THE CEREBRAL CORTEX UNDER EXPERIMENTAL CARCINOGENESIS

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Colorectal carcinogenesis remains one of the major challenges in experimental and clinical oncology. The aim of the study was to investigate morphological changes in the hemomicrocirculatory bed of the cerebral cortex in rats under conditions of experimental carcinogenesis. The study was performed on 30 outbred male white rats. The animals were divided into two groups: Group I consisted of 10 intact control animals, whereas Group II included 20 rats with experimentally induced colorectal adenocarcinoma in situ. Colorectal adenocarcinoma was induced using N,N-dimethylhydrazine hydrochloride dissolved in isotonic sodium chloride solution. The carcinogen was administered subcutaneously into the interscapular region at a dose of 7.2 mg/kg body weight once weekly for 30 weeks. It was established that experimental carcinogenesis induced pronounced alterative changes in the vessels of the microcirculatory bed of the cerebral cortex. Histologically, these alterations were manifested by uneven blood filling, blood stasis, erythrocyte sludge formation, and microthrombosis. Microvessels exhibited irregular blood filling, with signs of either dilation or marked vasospasm. The most prominent change was increased vascular permeability accompanied by the development of severe perivascular edema. The basement membrane was unevenly thickened, edematous, or condensed. Endothelial cells were swollen and vacuolated, exhibited hyperchromatic nuclei, and showed signs of desquamation.

Key words: hemocapillaries, arterioles, venules, microcirculatory system, histological changes, cerebral cortex, carcinogenesis.

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МІКРОСКОПІЧНІ ЗМІНИ СУДИН ГЕМОМІКРОЦИРКУЛЯТОРНОГО РУСЛА КОРИ ПІВКУЛЬ ГОЛОВНОГО МОЗКУ ЗА УМОВ ЕКСПЕРИМЕНТАЛЬНОГО КАНЦЕРОГЕНЕЗУ

Канцерогенез товстої кишки є однією з актуальних проблем експериментальної та клінічної онкології. Метою було вивчити морфологічні зміни гемомікроциркуляторного русла кори головного мозку щурів при експериментальному канцерогенезі. Дослід виконано на 30 аутбредних білих щурах самцях. Тварин було розділено на 2 групи: I – 10 контрольних тварин, II – 20 тварин з індукованою колоректальною аденокарциномою *in situ.* Для моделювання аденокарциноми використовували N,N-диметилгідразин гідрохлорид який розчиняли в ізотонічному розчині натрію хлориду. Канцероген вводили підшкірно в міжлопаткову область у дозуванні 7,2 мг/кг маси тіла тварин, один раз на тиждень протягом 30 тижнів. Встановлено, що за умов змодельованого онкогенезу у судинах мікроциркуляторного русла кори півкуль головного мозку щурів відбуваються альтеративні зміни, що проявляються нерівномірним кровонаповненням, стазами, сладж-ефектом, мікротромбами. Мікросудини нерівномірно кровонаповнені, з ознаками дилатації або різкого спазму. Найбільш вираженим є підвищення проникності стінки судин з розвитком значного периваскулярного набряку. Базальна мембрана нерівномірно потовщена, набрякла або ущільнена. Ендотеліоцити набряклі, вакуолізовані, з гіперхромними ядрами та ознаками десквамації.

Ключові слова: гемокапіляри, артеріоли, венули, мікроциркуляторне русло, гістологічні зміни, кора головного мозку, канцерогенез.

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Colorectal carcinogenesis remains a major challenge in modern experimental and clinical oncology owing to the high incidence of colorectal cancer and its systemic effects on the organism [6, 12–14]. Despite the localized nature of the neoplastic process at the early stages, particularly in carcinoma *in situ*, the development of neoplastic alterations is accompanied by significant disturbances in metabolism, hemodynamics, and microcirculation extending far beyond the primary lesion site [3, 5, 7, 10, 17]. Particular attention should be paid to changes in the central nervous system, since the brain is extremely sensitive to hypoxia, intoxication, and vascular disturbances [7, 11, 15, 17, 20].

It is well established that the vessels of the microcirculatory bed play a crucial role in maintaining trophic support and the functional state of nervous tissue. Structural alterations in hemocapillaries, arterioles, and venules lead to tissue hypoxia, increased permeability of the blood-brain barrier, cerebral edema, and dystrophic neuronal changes [15–17, 20]. During tumor progression, endothelial dysfunction represents one of the leading mechanisms of tissue injury and is associated with blood stasis, erythrocyte sludge formation, microthrombosis, and regional circulatory disturbances [5, 8, 11, 15–19].

Despite the considerable number of studies devoted to the morphological features of colorectal

carcinogenesis, alterations in the vessels of the microcirculatory bed of the cerebral cortex during experimental colorectal carcinogenesis *in situ* remain insufficiently investigated. Early microcirculatory disturbances are of particular interest because they may constitute the morphological basis for the development of secondary neurodystrophic processes within the central nervous system.

Therefore, investigation of histological changes in the vessels of the microcirculatory bed of the cerebral cortex under conditions of experimental colorectal carcinogenesis *in situ* is important for expanding current understanding of the pathogenetic mechanisms underlying the systemic effects of neoplastic processes and may provide a basis for the development of novel approaches to the prevention and correction of cerebrovascular disorders associated with oncopathology.

The purpose of the study was to investigate morphological alterations in the hemomicrocirculatory bed of the cerebral cortex in rats with experimentally induced colorectal adenocarcinoma.

Materials and methods. The experimental study was conducted on 30 outbred mature male white rats weighing 190±5 g. Animals were housed under standard vivarium conditions with free access to food and water. All experimental procedures complied with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986) [4]. The Bioethics Committee of I. Horbachevsky Ternopil National Medical University, Ministry of Health of Ukraine, confirmed compliance with ethical standards during the conduct of this study and reported no violations (Protocol No. 75, 01 November 2023).

Experimental animals were divided into two groups: Group I comprised 10 intact control rats, whereas Group II included 20 animals with experimentally induced colorectal adenocarcinoma *in situ*. Colorectal carcinogenesis was induced using N,N-dimethylhydrazine hydrochloride (Sigma-Aldrich Chemie, Japan, batch D161802) previously dissolved in isotonic sodium chloride solution. The carcinogen was administered subcutaneously into the interscapular region at a dose of 7.2 mg/kg body weight (calculated as active substance) once weekly for 30 weeks. At the end of the experiment, the presence of colorectal adenocarcinoma *in situ* was histologically verified in all animals of Group II.

Tissue sampling for histological examination was performed according to standard protocols [1]. Brain fragments were fixed in 96 % ethanol and 10 % buffered formalin solution. Subsequent histological processing was carried out using a LOGOS One automated tissue processor. Paraffin embedding and preparation of histological blocks were performed using a TEC2800 embedding station, after which serial sections were obtained with an AMR-400 rotary microtome.

Histological specimens were stained with hematoxylin and eosin, as well as according to the Nissl method using toluidine blue. Microscopic examination was performed using a MICROmed SEO SCAN light microscope. A Vision CCD Camera was used for photomicrography and documentation of histological specimens.

Results of the study. Histological examination of the cerebral cortex in intact animals demonstrated that the hemomicrocirculatory bed maintained normal structural organization without pronounced degenerative or alterative changes. A well-developed microvascular network was uniformly distributed across all cortical layers. Vessel walls were clearly delineated, and lumina were moderately filled with blood. Arterioles showed a well-organized wall structure and a moderate lumen without signs of hyperemia or dilation. Endothelial cells were elongated, resting on a distinct basement membrane, and contained normochromic nuclei. The tunica media was relatively thicker than the intima and composed of several layers of smooth muscle cells. The adventitia consisted of loose fibrous connective tissue without edema or inflammatory infiltration.

Hemocapillary walls were thin, with a narrow and uniform lumen. Endothelial cells were elongated and showed a typical structural organization with moderately basophilic nuclei. The basement membrane was continuous, without signs of edema or structural damage. Occasional erythrocytes were present within the lumen, whereas blood stasis, erythrocyte sludge formation, and thrombosis were absent. No perivascular edema was observed (Fig. 1).

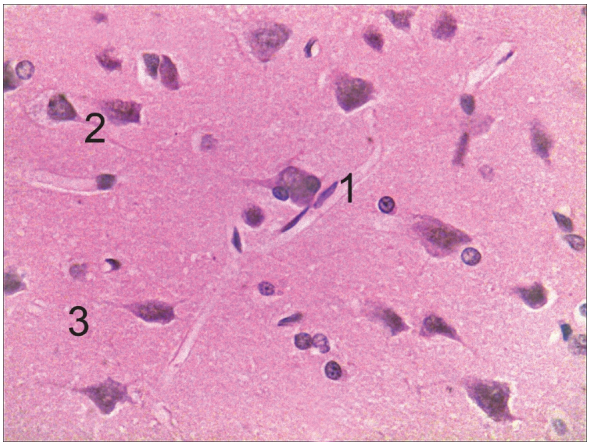
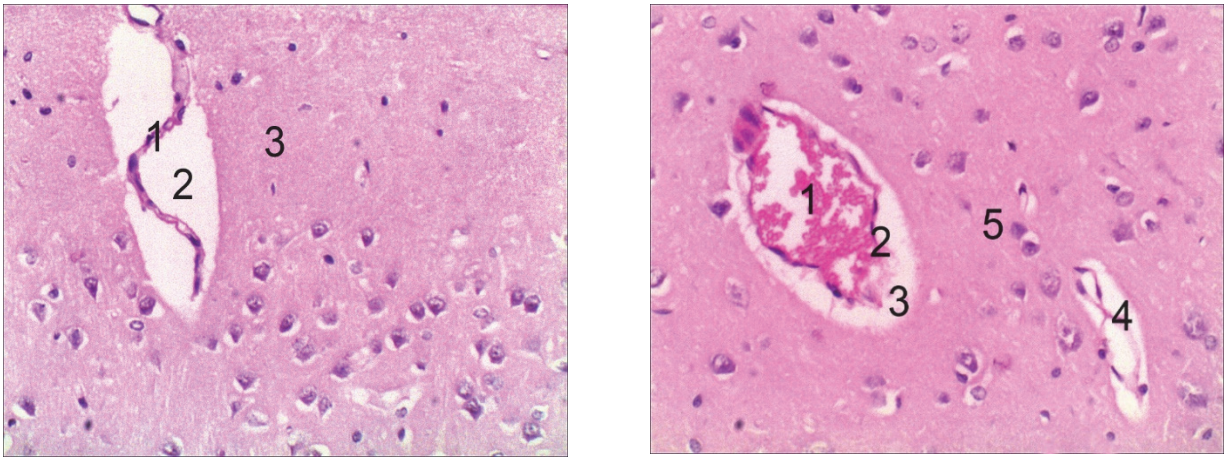


Fig. 1. Histological micrograph of a hemocapillary in the cerebral cortex of an intact laboratory rat. Hemocapillary (1), neurons (2), neuropil (3). Hematoxylin and eosin staining. ×400.

Venules exhibited moderately dilated, predominantly blood-filled lumina with thin and clearly outlined walls. The vascular wall was uniform and showed no signs of deformation. Blood cells were evenly distributed within the lumen without evidence of thrombus formation. Pronounced venous congestion was not observed. The adventitia

demonstrated no marked hydration or cellular infiltration. The topographic relationships between microvessels and the neuropil were preserved, with no signs of structural damage to nervous tissue components.

In the second experimental group, in which colorectal carcinogenesis *in situ* was induced, pronounced alterative changes were observed in the vessels of the microcirculatory bed of the cerebral cortex. These alterations were systemic in nature and appeared to be initiated by endothelial dysfunction, oxidative stress, hemodynamic disturbances, and chronic tissue hypoxia caused by the generalized pathological effects of carcinogenesis on the organism. Histological examination revealed uneven blood filling of the microcirculatory vessels within the cerebral cortex. Most venules and hemocapillaries were markedly congested and dilated. Significant deformation of the vascular walls was observed. Blood-filled capillaries were frequently localized in clusters, forming loci of venous congestion. In addition, some hemocapillaries demonstrated markedly narrowed and collapsed lumina accompanied by pronounced perivascular edema, indicating severe disturbances of cerebral microcirculation (Fig. 2. A).

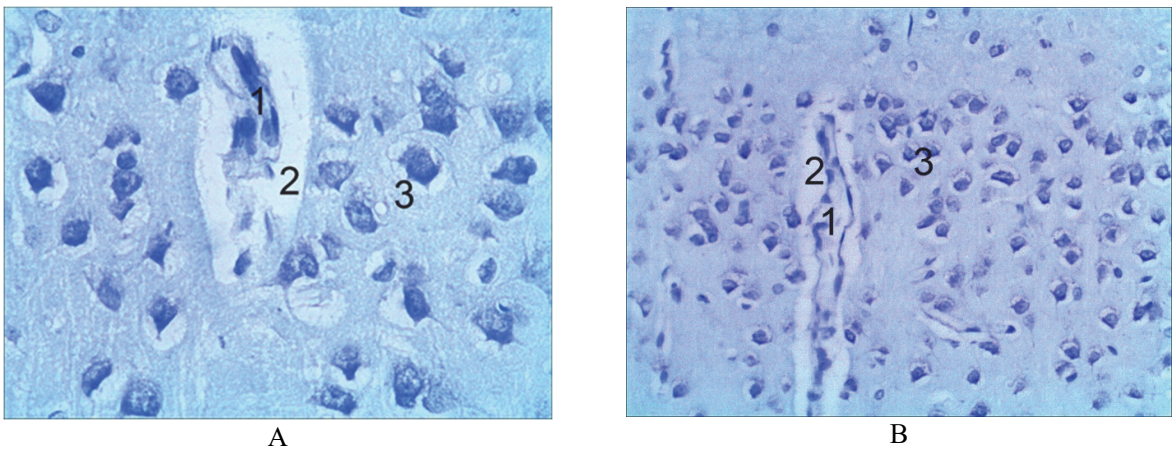


A B

Fig. 2. A – histological alterations of a hemocapillary in the cerebral cortex of a laboratory rat under experimentally induced carcinogenesis. Sharply collapsed hemocapillary (1), pronounced perivascular edema (2), neuropil (3). Hematoxylin and eosin staining. ×200. B – histological changes in a venule of the cerebral cortex of a laboratory rat under experimentally induced carcinogenesis. Blood-filled arteriole lumen (1), fragmented vascular wall (2), perivascular edema (3), hemocapillary (4), neuropil (5). Hematoxylin and eosin staining. ×400.

Signs of blood cell stasis and erythrocyte sludge phenomenon were predominantly observed in venules and, less frequently, in capillaries (Fig. 2.B). Erythrocyte borders were indistinct, with formation of aggregates indicative of impaired blood rheology and microcirculatory disturbances. Mixed thrombi were frequently observed within the lumina, predominantly in venular vessels.

Dystrophic alterations of endothelial cells were characterized by cellular swelling and poorly defined plasma membrane contours, particularly at the luminal aspect. Prominent cytoplasmic vacuolization and edema were observed. Nuclei were intensely basophilic, hyperchromatic, and pyknotic. Endothelial desquamation into the vascular lumen was frequently present. The basement membrane showed thickening, edema, homogenization, and condensation, and was frequently poorly defined (Fig. 3. A).



A B

Fig. 3. A – histological alterations of a hemocapillary in the cerebral cortex of a laboratory rat under experimentally induced carcinogenesis. Deformed hemocapillary wall (1), perivascular edema (2), neuropil and neurons (3). Nissl staining. ×400. B – histological changes in a hemocapillary of the cerebral cortex of a laboratory rat under experimentally induced carcinogenesis. Destructured hemocapillary wall (1), perivascular edema (2), neuropil (3). Nissl staining. ×200.

Marked perivascular edema was observed in all examined microscopic fields, associated with increased vascular permeability (Fig. 3.B). In some areas, severe tissue edema resulted in compression of the neuropil and adjacent neurons, particularly around hemocapillaries and venules.

Arterioles exhibited pronounced dystrophic alterations. Lumina were markedly narrowed, while the vascular wall was deformed and thickened. Smooth muscle cells of the tunica media were swollen, with weakly eosinophilic cytoplasm and hyperchromatic nuclei. Some arterioles were blood-filled and showed increased vascular permeability (Fig. 4). In some areas, glial cell proliferation was noted adjacent to dystrophically altered microvessels, indicating reactive cerebral cortex changes. Microcirculatory disturbances were frequently associated with neuropil damage, particularly near vessels with marked venous congestion and stasis.

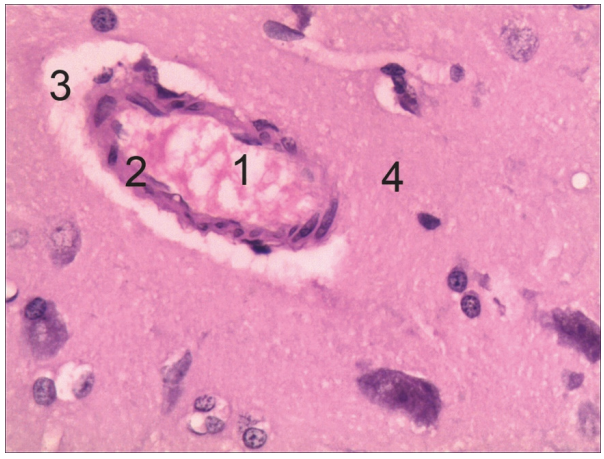


Fig. 4. Histological alterations of arteriole in the cerebral cortex of a laboratory rat under experimentally induced carcinogenesis. Arteriole lumen (1), destructured vascular wall (2), perivascular edema (3), neuropil (4). Hematoxylin and eosin staining. ×400.

Discussion. Histological examination of the cerebral cortex in white laboratory rats with experimentally induced colorectal carcinogenesis *in situ* revealed pronounced structural alterations of the hemomicrocirculatory bed. These changes were systemic in origin and indicated a significant impact of the neoplastic process on the central nervous system, particularly the cerebral cortex, even under conditions of localized neoplasia. The obtained findings are consistent with published data describing oncogenesis as a multisystemic pathomorphological process associated with the development and progression of hypoxia, impaired blood coagulation, and marked endothelial dysfunction [5, 6, 8, 15, 17].

Histologically, the most pronounced alterations in the cerebral cortical microvascular bed included uneven vascular filling, venous congestion, blood stasis, thrombosis, and erythrocyte sludge formation. Such remodeling of the microcirculatory bed represents a typical vascular response in oncopathological conditions. Current evidence indicates that carcinogenesis is accompanied by activation of the coagulation cascade, alterations in hemorheological properties of blood, and microthrombus formation, all of which impair tissue perfusion and increase the risk of ischemic injury in various organs, including the brain [8, 11, 15–17, 20].

One of the key alterations observed was endothelial dystrophy accompanied by structural damage to the endothelial lining. Endothelial cell swelling, desquamation into the capillary lumen, as well as edema and thickening of the basement membrane, indicate the development of endothelial dysfunction. Beyond forming the vascular lining, endothelial cells perform essential regulatory functions, including the synthesis of vasoactive mediators, the regulation of hemostasis, and the control of vascular permeability. Endothelial injury leads to profound microcirculatory disturbances and increased permeability of the blood-brain barrier. Contemporary literature confirms that oncogenesis is associated with the systemic circulation of proinflammatory cytokines and tumor-derived metabolic products, which induce vascular wall injury and contribute to chronic vascular insufficiency and subsequent multiorgan dysfunction [6, 10, 15, 16, 18, 19].

Pronounced perivascular edema and erythrocyte diapedesis confirmed increased permeability of the vascular wall. Expansion of the perivascular spaces was accompanied by neuronal compression and progressive hypoxic alterations. Similar patterns of microcirculatory dysfunction and increased vascular permeability in the hemomicrocirculatory bed have been reported in studies addressing cerebrovascular alterations in systemic pathological conditions and oncogenesis [5, 6, 9, 10, 15].

Pronounced alterations of the cerebral microvascular bed were also accompanied by degenerative changes in nervous tissue. In neurons of the cerebral cortex, signs of hyperchromasia or hypochromasia and chromatolysis were observed, reflecting hypoxic–ischemic injury. Published studies indicate that these changes are induced by chronic hypoxia and are associated with neuronal depletion, activation of oxidative stress, and progression of neurodegenerative processes in nervous tissue [2, 11].

Accumulating evidence confirms the key role of neuroinflammation in the development of neuronal injury during carcinogenesis. Neuroglial cells play a central role in this process, representing an early compensatory-adaptive response; however, with chronic persistence of the pathological stimulus, this response contributes to progressive neurodegenerative changes [3, 9, 11, 13].

Conclusion

In white laboratory rats with experimentally induced colorectal carcinogenesis *in situ*, significant destructive and degenerative alterations were observed in the cerebral cortical microcirculatory bed. These changes included blood stasis, erythrocyte sludge formation, venous congestion, microthrombosis, and endothelial desquamation. Markedly increased vascular permeability accompanied by severe perivascular edema was also observed. The findings indicate that localized colorectal carcinogenesis *in situ* induces systemic alterations, particularly in the cerebral cortex, resulting in tissue hypoxia, microcirculatory disturbances, and neurodystrophic changes.

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Conflict of interest. The authors have no conflicts of interest to declare.

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