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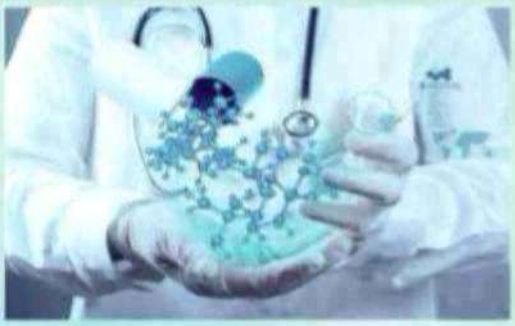

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COMPARATIVE CHARACTERISTICS OF THE MORPHOLOGY OF EXPERIMENTAL BREAST CANCER WITH LUNG METASTASIS

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✓ ***Resume***

Metastasis is the final stage of malignant progression; theoretically, a tumor of any size has metastatic potential. The biological nature of cancer and the characteristics of the host determine the possibility of further disease progression even after radical treatment. According to several authors, 12 to 30% of all lung and pleural tumors are metastatic. This review focuses on the comparative morphology of experimental breast cancer with lung metastasis.

Keywords: breast cancer, metastasis, lungs, immunohistochemical markers, morphology, morphometry.

СРАВНИТЕЛЬНАЯ ХАРАКТЕРИСТИКА МОРФОЛОГИИ ЭКСПЕРИМЕНТАЛЬНОГО РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ ПРИ МЕТАСТАЗИРОВАНИИ В ЛЕГКИЕ

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✓ ***Резюме***

Метастазирование является заключительным этапом развития злокачественного процесса, теоретически опухоль любых размеров имеет метастатический потенциал. Биологическая природа рака и особенности организма с опухолью предопределяют возможность дальнейшего развития заболевания даже после радикально проведенного лечения. По данным ряда авторов, от 12 до 30% всех опухолевых поражений легких и плевры являются метастатическими. Этот обзор посвящается на сравнительная характеристика морфологии экспериментального рака молочной железы при метастазировании в легкие.

Ключевые слова: рака молочной железы, метастазирования, легкие, иммуногистохимические маркеры, морфология, морфометрия.

EKSPERIMENTAL SUT BEZI SARATONINING O‘PKAGA METASTAZLANISHIDAN KEYINGI MORFOLOGIYASINING QIYOSIY TAVSIFI

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✓ ***Rezyume***

Metastaz – xavfli jarayonlar rivojlanishning yakuniy bosqichi bo'lib; nazariy jihatdan, har qanday o'lchamdagi o'simta metastatik salohiyatga ega. Saratonning biologik tabiati va uy egasining xususiyatlari, hatto radikal davolashdan keyin ham kasallikning keyingi rivojlanish imkoniyatini aniqlaydi. Bir nechta mualliflarning fikriga ko'ra, barcha o'pka va plevra o'smalarining 12-30% metastatikdir. Ushbu sharh eksperimental sut bezi saratonining o'pka metastazlari bilan qiyosiy morfologiyasiga qaratilgan.

Kalit so'zlar: sut bezi saratoni, metastaz, o'pka, immunogistokimyoviy markerlar, morfologiya, morfometriya.

Relevance

Breast cancer is a disease in which cancer cells form in the breast tissue. The risk of developing breast cancer is increased by a family history, hereditary changes, and other factors. A risk factor is anything that increases the likelihood of developing the disease. Risk factors for developing breast cancer include: a history of breast cancer, a benign (non-cancerous) breast disease; a family history of breast cancer in a first-degree relative (mother, daughter, or sister); inherited changes in the BRCA1 or BRCA2 genes or other genes; and other factors [1].

According to GLOBOCAN, approximately 2.1 million new cases of breast cancer were registered among women worldwide in 2018, accounting for nearly 1 in 4 cancer cases among women. The incidence rate is higher in economically developed countries, while mortality is highest in less economically developed countries. The highest incidence rates of breast cancer are found in Australia, New Zealand, Northern Europe (the UK, Sweden, Finland, and Denmark), Western Europe (Belgium, the Netherlands, and France), Southern Europe (Italy), and North America [2].

Metastasis is the final stage of malignant progression; theoretically, a tumor of any size has metastatic potential. The biological nature of cancer and the characteristics of the host determine the likelihood of further disease progression even after radical treatment. According to several authors, 12 to 30% of all lung and pleural tumors are metastatic [8].

Breast cancer has a distinct metastatic pattern, typically affecting the bones, liver, lungs, and brain. The development of breast cancer metastases in any given organ is a complex process dependent on multiple factors, the most important of which is the tumor's molecular subtype. There are four subtypes of breast cancer, depending on gene expression, ER, PR, HER2 status, and proliferation status, which is determined by the Ki-67 proliferative activity index. In increasing tumor aggressiveness, there are luminal subtype A (ER+/PR+), luminal subtype B (ER+/PR+/HER2–/+/Ki-67+), HER2-overexpressing subtype (ER–/PR–/HER+), and basal-like/triple-negative (TN) subtype (ER–/PR–/HER2–). Breast cancer of the TN subtype has the greatest tendency to metastasize to the lungs (32%), while luminal A/B (21%) and HER2+ (25%) subtypes have a lower tendency [4].

Tumor metastasis typically consists of several sequential stages, including the emergence of the primary tumor from surrounding tissues, intravasation into blood and/or lymphatic vessels with the formation of circulating tumor cells, extravasation followed by dissemination and transformation of tumor cells to form a metastasis. The development of breast cancer metastases to the lungs is determined by many factors. A number of genes have been identified that contribute to the formation of micro- and macrometastases in the lungs. These include the BMP (bone morphogenetic protein) inhibitor Coco, the differentiation inhibitor proteins, and the DNA binding inhibitors ID1 and ID3; the gene encoding the extracellular matrix protein tenascin C, CXCL1 (chemokine (C–X–C motif) ligand 1), vascular cell adhesion molecule 1 (VCAM 1), as well as the gene for fine-tuning epithelial-mesenchymal transition and circulating cancer biomarkers microRNA (miR 200) [5].

For example, Coco, a transforming growth factor b (TGF b) ligand antagonist overexpressed by metastatic cells, activates dormant breast cancer cells to form repeated colonies in lung tissue [6]. Metastatic breast cancer cells initiate the expression of TGF b, followed by the release of periostin, an extracellular matrix protein, and activation of the Wnt signaling pathway, which promotes the development of lung metastases. The glycoprotein tenascin C promotes the activation of the Notch pathway and supports breast cancer cell growth. VCAM 1 promotes the protection of breast cancer cells from apoptosis [5]. ID1 promotes the colonization and sustained proliferation of metastatic cells in the lungs of patients with the TN subtype of breast cancer [7].

The development of metastases in lung tissue is facilitated by the formation of so-called premetastatic niches (PMN). External factors, including smoking and prolonged exposure to environmental pollutants, play a significant role in these processes. Long-term exposure to pollutants and cigarette smoke negatively impacts both the innate and adaptive immune systems. Nicotine stimulates metastasis progression, although it is not an oncogene. Chronic nicotine exposure promotes the formation of PMNs in the lungs through the activation of signal transducer and activator of transcription-3 (STAT3), serine/threonine protein kinase B (Akt), and NF-κB (nuclear factor κB). This releases pro-tumor N2 neutrophils, which secrete STAT3-activated lipocalin 2 (LCN2), stimulating metastasis colonization and growth. LCN2 has been shown to persist long-term in the lungs of rats exposed to cigarette smoke and in the plasma of smoking patients [11].

Studies also confirm the effects of cigarette smoke on immunosuppression by reducing natural killer (NK) cell activity, macrophage antigen activity, dendritic cell counts, and T-cell proliferation [12]. Cigarette smoking increases the risk of metastases by 18% and reduces survival at diagnosis by 33% [9].

In addition to external factors, vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF), and TGF-β are involved in the development of PMN. The role of CSF3 (colony-stimulating factor 3), secreted by tumor cells, and CCL2 (chemokine (C–C motif) ligand 2) in the formation of PMN has been demonstrated by recruiting inflammatory monocytes and macrophages, which facilitate the release of circulating tumor cells from the vascular bed, or by inhibiting NK cell maturation [14, 18].

Hypoxia also stimulates rapid tumor cell growth. Premetastatic effects of chemotherapy drugs such as taxanes and anthracyclines have been described, despite their effectiveness in the treatment of breast cancer [21].

A number of studies have found that neutrophils are capable of supporting the development of metastases, and the expression of leukotrienes promotes the colonization of distant organs and tissues. A study by J. Park et al. demonstrated the dependence of neutrophils on leukotrienes and arachidonate-5-lipoxygenase, which maintains active metastatic cells [22]. This is important for the development of new antitumor drugs. The ability of neutrophils to form traps influences tumor metastasis by stimulating the invasion and migration of tumor cells [23].

Activation of the TNF-α signaling pathway significantly influences the development of breast cancer metastases to the lungs. In a study by J. Berthelet et al., TNF-α levels were higher in lung metastases than in the liver. Interleukin-11 and VEGF-D also promote the polyclonal growth of lung metastases. The efficacy of the TNF-α inhibitor etanercept and the apoptosis protein inhibitor birinapant in the treatment of breast cancer metastases was assessed in an experimental model. Etanercept significantly reduced the Shannon diversity index in breast cancer lung metastases without affecting subclonal survival. Birinapant, whose action also depends on TNF-α, eliminated breast cancer metastases in the lungs and liver, i.e., it proved to be highly effective in reducing the metastatic burden [25]. These results suggest the high future clinical potential of these drugs in the treatment of patients with metastatic breast cancer [24].

Mechanisms of Metastasis. Metastasis is associated with disruption of the normal regulation of cell growth and cell death (apoptosis). This process involves various molecules, such as cadherins and metalloproteinases, which promote the breakdown of the extracellular matrix. Genetic alterations, including the activation of oncogenes (e.g., HER2) and the inactivation of tumor suppressors, play a significant role in the development of aggressive tumor behavior. These molecules are emerging as potential targets for new therapeutic strategies [15].

According to Росяйкина Я. А., Дерябина О. Н. (2025): Main sites of breast cancer metastases of lung metastases: The metastasis rate is 21%. Surgical treatment is possible in no more than 5-10% of patients. Five-year survival rates after surgery reach 30-42% [10].

Lung metastases, in particular, tend to occur within 5 years of the initial diagnosis of breast cancer and have a significant impact on patient morbidity and mortality. Physiologically, these metastases disrupt normal lung function, leading to coughing, difficulty breathing, hemoptysis, and ultimately death. Lung metastases remain difficult to treat, and an estimated 60–70% of patients dying from breast cancer have lung metastases. For patients with metastases confined solely to the lungs, the

prognosis is extremely poor, with a median survival of only 25 months. This unfavorable outcome is explained by the limited number of treatment options associated with inoperable lesions [17].

The lung is the first major capillary bed encountered by breast cancer cells after entering the bloodstream. As tumor cells circulate through the lungs, they can come into contact with up to 100 m2 of superficial vasculature. Because these tumor cells are approximately five times larger than the extremely narrow pulmonary capillaries, the likelihood of breast cancer cells becoming trapped in these capillary beds and subsequently extravasating into lung tissue is high. Pulmonary capillaries are composed of endothelial cells encapsulated by the basement membrane and adjacent alveolar cells. To facilitate transendothelial migration and extravasation, the tumor must express cell surface markers specific to the lung microenvironment. However, although extravasation can occur quite easily through these physical processes, the ability of individual metastatic cells to successfully transition into micrometastases and subsequently progress to macrometastases is quite rare. Thus, these final events represent the rate-limiting steps of metastasis, which depend on optimal interactions between the "seed" and "soil" [19].

Cancer-related mortality is primarily due to metastatic recurrence in distant organs. The time to the development of hematogenous metastases depends on the type of cancer and can vary significantly. For example, metastatic recurrence in lung cancer can occur within a few weeks, while in colorectal cancer, it can take several years. The insidious nature of breast cancer is that the period of distant recurrence in breast cancer can range from several months to decades after surgery [20]. Although the risk of distant metastases in breast cancer patients is almost 10–20%, all patients receive adjuvant systemic therapy after surgery and radiation therapy to reduce the risk of distant metastases. Thus, most patients do not develop distant metastases and are likely to suffer unnecessarily from the systemic toxic side effects of chemotherapy [3].

Conclusion

Metastasis formation was long believed to be a stochastic process, with the direction of metastasis determined by the anatomical features of blood and lymphatic drainage from the primary tumor. Indeed, anatomical features can fully explain, for example, the spread of tumor cells to regional lymph nodes or the occurrence of hematogenous metastases from colorectal cancer to the liver. However, the occurrence of metastases to the bone marrow in kidney cancer or to the lungs in breast cancer cannot be explained solely by blood flow characteristics.

Predicting the location of future metastases will allow physicians to focus on a specific organ for earlier detection of hematogenous metastases. Therefore, the ability to assess the risk of occurrence and location of future metastases will enable a personalized approach to treatment for cancer patients.

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