SUT BEZI INFILTRATSIYALOVCHI SARATONIDA LIMFOGEN METASTAZLARNING MORFOLOGIK XUSUSIYATLARI

Alimxodjayeva Lola Telmonovna - *Respublika ixtisoslashtirilgan onkologiya va radiologiya ilmiy amaliy tibbiyot markazi, t.f.d., professor. - ORCID: 0009-0003-3625-0135, E-mail:* lola.alimkhodjaeva@mail.ru

Ruziyev Sherzod Ibodullayevich - *Respublika sud-tibbiy ekspertiza ilmiy-amaliy markazi direktori, t.f.d., professor.*

Ahmadjanova Orifa Maxmudovna - *Respublika ixtisoslashtirilgan onkologiya va radiologiya ilmiy-amaliy tibbiyot markazi Namangan filiali, PhD talabasi.*

***Abstract.* Objective:** *To investigate the morphological characteristics of lymphogenous metastasis in infiltrating breast cancer, focusing on the immunomorphological status of metastatic and non-metastatic lymph nodes with or without germinal centers.* **Methods:** *Lymph nodes from breast cancer patients were evaluated histologically and immunomorphologically, comparing nodes with germinal centers to those without. The study included 161 lymph node samples, divided into metastatic and non-metastatic groups. Quantitative indicators such as sinus histiocytosis, lymphocytosis, and presence of fibrosis were assessed. Correlations were analyzed in relation to menopausal status and degree of lymph node replacement by metastases.* **Results:** *Non-metastatic lymph nodes lacking germinal centers demonstrated significantly higher marginal sinus histiocytosis and sinus lymphocytosis (p = 0.01). A moderate correlation was found between sinus histiocytosis in partially metastatic lymph nodes (10–50% replacement) and non-metastatic nodes without germinal centers in postmenopausal women (r = 0.4; p = 0.04). The presence of germinal centers in metastatic lymph nodes was not significantly associated with their presence in non-metastatic nodes. Four distinct histological patterns were identified depending on the combination of germinal center presence across both node types.* **Conclusion:** *Assessing the distribution of germinal centers in both metastatic and non-metastatic nodes could aid in understanding tumor-host immune interactions and contribute to improved stratification of breast cancer patients.*

Key word: *lymphogenus metastases, infiltrating breast cancer, germinal center*

Annotatsiya. Maqsad: *Sut bezi infiltratsiyalovchi saratonida limfogen metastazlarning morfologik xususiyatlarini oʻrganish, germinativ markazlari mavjud yoki mavjud boʻlmagan metastatik va metastatik boʻlmagan limfa tugunlarining immunomorfologik holatiga eʼtibor qaratish.* **Material va metod:** *Sut bezi saratoni bilan ogʻrigan bemorlarning limfa tugunlari gistologik va immunomorfologik jihatdan baholandi, germinativ markazlari mavjud tugunlar germinativ markazlari yoʻq tugunlar bilan taqqoslandi. Tadqiqotda 161 ta limfa tuguni namunasi metastatik va metastatik boʻlmagan guruhlarga ajratildi. Sinus gistiotsitozi, limfotsitoz va fibroz mavjudligi kabi miqdoriy koʻrsatkichlar baholandi. Menopauza holati va limfa tugunlarining metastazlar bilan toʻlish darajasi oʻrtasidagi bogʻliqliklar tahlil qilindi.* **Natijalar:** *Germinativ markazlari boʻlmagan metastatik boʻlmagan limfa tugunlarida marginal sinus gistiotsitozi va sinus limfotsitozi sezilarli darajada yuqori boʻldi (p = 0,01). Menopauzadan keyingi davrdagi ayollarda qisman metastatik limfa tugunlaridagi sinus gistiotsitozi (10-50% toʻlish) va germinativ markazlari boʻlmagan metastatik boʻlmagan tugunlar oʻrtasida oʻrtacha bogʻliqlik aniqlandi (r = 0,4; p = 0,04). Metastatik limfa tugunlarida germinativ markazlarning mavjudligi ularning metastatik boʻlmagan tugunlardagi mavjudligi bilan sezilarli darajada bogʻliq emas edi. Ikkala turdagi tugunlarda germinativ markaz mavjudligining kombinatsiyasiga*

qarab to'rtta aniq gistologik namuna aniqlandi. **Xulosa:** *Metastatik va metastatik bo'lmagan tugunlarda germinativ markazlarning taqsimlanishini baholash o'sma-xo'jayin immun o'zaro ta'sirini tushunishga yordam berishi va sut bezi saratoni bilan og'rigan bemorlarni tabaqalashtirishni yaxshilashga hissa qo'shishi mumkin.*

Kalit so'zlar: *limfogen metastazlar, infiltratsiyalovchi sut bezi saratoni, germinativ markaz*

Аннотация. **Цель:** *Изучить морфологические особенности лимфогенных метастазов при инфильтрирующем раке молочной железы, сосредоточившись на иммуноморфологическом статусе метастатических и неметастатических лимфатических узлов с герминативными центрами или без них.* **Методы:** *Лимфатические узлы больных раком молочной железы оценивали гистологически и иммуноморфологически, сравнивая узлы с герминативными центрами с узлами без них. В исследование было включено 161 образец лимфатических узлов, разделенных на метастатические и неметастатические группы. Оценивались количественные показатели, такие как гистиоцитоз синусов, лимфоцитоз и наличие фиброза. Корреляции были проанализированы в зависимости от менопаузального статуса и степени замещения лимфатических узлов метастазами.* **Результаты:** *Неметастатические лимфатические узлы без герминативных центров демонстрировали значительно более высокий краевой синусовый гистиоцитоз и синусовый лимфоцитоз (р = 0,01). Была обнаружена умеренная корреляция между синусовым гистиоцитозом в частично метастатических лимфатических узлах (10-50% замещения) и неметастатическими узлами без герминативных центров у женщин в постменопаузе (r = 0,4; p = 0,04). Наличие герминативных центров в метастатических лимфатических узлах существенно не ассоциировалось с их наличием в неметастатических узлах. Были выявлены четыре различных гистологических паттерна в зависимости от сочетания наличия герминативных центров в обоих типах узлов.* **Заключение:** *Оценка распределения герминативных центров как в метастатических, так и в неметастатических узлах может помочь понять иммунные взаимодействия между опухолью и организмом и способствовать улучшению стратификации пациентов с раком молочной железы.*

Ключевые слова: *лимфогенные метастазы, инфильтрирующий рак молочной железы, герминативный центр.*

Introduction. *Breast cancer remains the most frequently diagnosed malignancy among women worldwide and is a leading cause of cancer-related mortality[9-11]. Infiltrating breast cancer (IBC), particularly invasive ductal carcinoma (IDC), constitutes the most common histological subtype, accounting for approximately 70–80% of all cases [1,2]. Despite significant advancements in diagnostic and therapeutic strategies, patient outcomes vary widely due to the heterogeneous biological behavior of the disease[7].*

Morphological predictors, including tumor size, histological grade, lymphovascular invasion, and patterns of stromal reaction, have long been considered key determinants of tumor aggressiveness and metastatic potential [12,13]. Accurate histopathological assessment provides critical prognostic information and guides treatment planning, especially in resource-limited settings where molecular profiling may not be readily accessible.

Recent studies have emphasized the prognostic significance of morphological parameters such as nuclear pleomorphism, mitotic count, and architectural patterns, which correlate with tumor proliferation, hormone receptor status, and recurrence risk [4,14]. Moreover, integrating

traditional morphological features with immunohistochemical markers like Ki-67, ER, PR, and HER2 further enhances risk stratification and personalized treatment approaches [3].

The majority of IBC cases are classified as invasive ductal carcinoma (IDC), a histological subtype characterized by its aggressive biological behavior and high propensity for regional and distant metastases [13]. Among the various mechanisms of tumor dissemination, lymphogenous metastasis plays a central role in disease progression and is a key determinant of patient prognosis. Lymph node involvement is a pivotal component of the TNM staging system and has long been recognized as one of the most powerful prognostic factors in breast cancer . The presence, number, and extent of axillary lymph node metastases significantly influence therapeutic decisions, including the need for adjuvant chemotherapy, radiotherapy, and targeted treatments [4]. Despite this clinical importance, the morphological patterns and histological features of lymph node metastases have not been fully elucidated and remain underexplored in standard pathological evaluations. Recent evidence suggests that the morphological characteristics of metastatic foci within lymph nodes—such as the size and architecture of tumor cell clusters, sinusoidal infiltration patterns, the presence or absence of germinal centers, and associated immune responses—may carry additional prognostic significance beyond the binary presence or absence of metastasis [9]. Histopathological examination of non-metastatic lymph nodes has also revealed reactive changes, including sinus histiocytosis, follicular hyperplasia, and paracortical expansion, which may reflect the host immune response and tumor burden [5].

In this study, we aim to evaluate the morphological features of lymphogenous metastases in patients with infiltrating breast cancer, focusing on histological architecture, sinus involvement, germinal center activity, and associated immunomorphological markers. Understanding these patterns may refine prognostic models and enhance personalized treatment planning for breast cancer patients.

Materials and methods. *This study included a total of 161 lymph node specimens obtained from patients diagnosed with infiltrating breast cancer exhibiting lymphogenous metastases. Lymph nodes were histologically categorized into metastatic and non-metastatic groups. Further subdivision was based on the presence or absence of germinal centers in non-metastatic lymph nodes.*

Histological and Immunomorphological Assessment:

All lymph node samples underwent standard hematoxylin and eosin (H&E) staining, followed by immunomorphological evaluation under light microscopy. The presence of germinal centers, sinus histiocytosis (both marginal and medullary), sinus lymphocytosis, sinus fibrosis, lipomatosis, postcapillary venules, and capsule infiltration were semi-quantitatively scored on a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe).

Patient Stratification:

Patients were stratified based on menstrual status (premenopausal or postmenopausal) and extent of lymph node involvement by metastases. Metastatic lymph nodes were further divided according to the degree of parenchymal replacement by tumor cells: up to 10%, 10–50%, 50–75%, and 100%.

Statistical Analysis:

Comparative analysis between groups (lymph nodes with vs. without germinal centers) was performed using the Student's t-test or χ^2 test, as appropriate. Correlation between sinus histiocytosis in metastatic and non-metastatic nodes was evaluated using Pearson's correlation coefficient. Statistical significance was set at $p < 0.05$.

Result. *When analyzing the tissue condition of lymph nodes not affected by metastases, two categories were identified: lymph nodes with germinal centers and those without. The morphological structure of these lymph node types differed slightly. Regardless of menstrual*

function status, lymph nodes without germinal centers exhibited more pronounced marginal sinus histiocytosis and sinus lymphocytosis (Table 1).

Table 1. *Immunomorphological Status of Non-metastatic Lymph Nodes in Patients with Lymphogenous Metastases (Regardless of Menstrual Function)*

Parameter	With Germinal Centers (n=52)	Without Germinal Centers (n=109)	*P*
Marginal sinus histiocytosis	*1.8 ± 0.9*	*2.2 ± 1.1*	*0.01*
Medullary sinus histiocytosis	*2.1 ± 0.9*	*2.3 ± 1.2*	*0.14*
Sinus lymphocytosis	*2.0 ± 1.2*	*2.5 ± 1.3*	*0.01*
Sinus fibrosis	*1.3 ± 0.6*	*1.3 ± 0.6*	*0.50*
Postcapillary venules	*1.4 ± 0.9*	*1.3 ± 0.6*	*0.20*
Capsule infiltration	*1.2 ± 0.6*	*1.2 ± 0.6*	*0.50*
Lipomatosis	*1.5 ± 0.7*	*1.5 ± 0.7*	*0.50*

Additionally, in postmenopausal patients, a direct correlation was observed between the degree of sinus histiocytosis in metastatic lymph nodes (with 10–50% replacement) and the intensity of sinus histiocytosis in non-metastatic lymph nodes without germinal centers (r = 0.4; p = 0.04). Irrespective of menstrual function, the frequency of germinal centers in metastatic lymph nodes with ≤10% or 10–50% replacement did not depend on the presence of germinal centers in non-metastatic lymph nodes (Table 2).

Table 2. *Germinal Center Presence in Metastatic Lymph Nodes Based on the Status of Non-metastatic Lymph Nodes (Regardless of Menstrual Function)*

Feature		Lymp node (negative status)	
		With Germinal Centers	*Without Germinal Centers*
Germinal centers in ≤10% replaced nodes	*no*	*12/26 (46%)*	*23/45 (51%)*
	yes	*14/26 (54%)*	*22/45 (49%)*
	X² = 0,2; p = 0,69		
Germinal centers in 10-5% replaced nodes	*no*	*14/20 (70%)*	*21/34 (62%)*
	yes	*6/20 (30%)*	*13/34 (38%)*
	X² = 0,3; p = 0,54		

Patients with metastatic lymph nodes showing 10–50% replacement were divided into four groups based on the presence or absence of germinal centers in both metastatic and non-metastatic nodes:

• *Group I (29.0%): Germinal centers present in both metastatic and non-metastatic nodes (GC⁺/GC⁺)*

• *Group II (14.5%): No germinal centers in either metastatic or non-metastatic nodes (GC⁻/GC⁻)*

• *Group III (36.0%): Germinal centers absent in metastatic nodes but present in non-metastatic ones (GC⁻/GC⁺)*

• *Group IV (20.5%): Germinal centers present in metastatic nodes but absent in non-metastatic ones (GC⁺/GC⁻)*

Among patients with lymph nodes replaced by 50–75% or completely (100%), three groups were identified based on germinal center presence in non-metastatic nodes):

• *Group I (6.3%): All non-metastatic nodes had germinal centers (GC-All⁺)*

• *Group II (68.7%): No germinal centers in any non-metastatic nodes (GC-All⁻)*

• *Group III (25%): Germinal centers present in some but not all non-metastatic nodes (GC-Mixed)*

Discussion and conclusion. *The immunomorphological profile of lymph nodes in infiltrating breast cancer exhibits significant variation based on the presence of germinal centers and metastatic involvement. These variations are influenced by menopausal status and may have diagnostic or prognostic value. Assessing the distribution of germinal centers in both metastatic and non-metastatic nodes could aid in understanding tumor-host immune interactions and contribute to improved stratification of breast cancer patients.*

The immunomorphological analysis of lymph nodes in infiltrating breast cancer reveals meaningful variations that correlate with both the presence of germinal centers and the extent of metastatic involvement. These morphological differences, particularly in the architecture of lymphoid tissues and the activation status of germinal centers, may reflect underlying tumor-host immune dynamics. Notably, our findings suggest that menopausal status may modulate these histological patterns, implying a potential hormonal influence on immune system activity within regional lymphatic structures [6].

The observed differences between metastatic and non-metastatic lymph nodes underscore the complexity of the tumor microenvironment and its immunological response. Nodes with preserved or reactive germinal centers, especially in the absence of metastasis, may indicate a more active local immune surveillance mechanism, whereas those with disrupted or absent germinal architecture in metastatic contexts may reflect tumor-mediated immune suppression or evasion [9]. These patterns are not only histologically distinct but may also carry prognostic significance, offering insights into tumor biology beyond conventional staging parameters.

Incorporating the assessment of germinal center distribution and immunomorphological features into routine pathological evaluation may enhance diagnostic precision and provide supplementary prognostic information. Such evaluation could be particularly beneficial in stratifying patients with ambiguous or borderline nodal involvement, aiding in treatment planning and follow-up strategies. Furthermore, this approach may help identify patients who could benefit from immunomodulatory or adjuvant therapies based on the immune architecture of their lymph nodes [5].

Overall, the integration of morphological and immunological criteria in the evaluation of lymph nodes contributes to a more nuanced understanding of breast cancer progression and

supports the development of personalized oncologic care. Future studies with larger cohorts and molecular correlation are warranted to validate these findings and explore their translational potential in clinical practice.

References:

1. *Alimkhodjayeva, L. T., Mirzayeva, M. A., Zakirova, L. T., & Norbekova, M. X. (2023). The Effect of Body Mass Index on the Clinical and Morphological Characteristics of Breast Cancer in Women with Metabolic Syndrome. American Journal of Medicine and Medical Sciences, 13(8), 1118-1122..*

2. *Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.*

3. *Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst. 2009;101(10):736–50. doi:10.1093/jnci/djp082.*

4. *Geyer FC, Rodrigues DN, Weigelt B, Reis-Filho JS. Molecular classification of breast cancer—quotidian practice and translational implications. Adv Anat Pathol. 2012;19(1):26–38.*

5. *Giuliano, A. E., McCall, L., Beitsch, P., et al. (2011). Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: The ACOSOG Z0011 randomized trial. JAMA, 305(6), 569–575.*

6. *Ginter, P. S., & Hoda, S. A. (2002). Histopathological changes in non-metastatic axillary lymph nodes in breast cancer. Modern Pathology, 15(6), 641–646.*

7. *Lola T. Alimkhodjaeva, & Munira H. Norbekova. (2022). CLINICAL SIGNIFICANCE OF THE DENSITY OF TUMOR MICROVESSELS IN BREAST CANCER IN MEN. Central Asian Journal of Medicine, (1), 97-104. Retrieved from https://www.journals.tma.uz/index.php/cajm/article/view/495*

8. *Matluba A. Mirzaeva, Bakhtiyor U. Iriskulov, & Lola T. Alimkhodjaeva. (2023). HISTOLOGICAL PRESENTATION OF BREAST CANCER AND ITS ASSOCIATION WITH METABOLIC SYNDROME. Central Asian Journal of Medicine, (4), 44-51.*

9. *Marchiò, C., Sapino, A., & Bussolati, G. (2017). Micromorphological patterns of lymph node metastases in breast cancer: Implications for clinical practice. Histopathology, 70(4), 545–554.*

10. *Mirzaeva, M., & Irmatova, G. (2024). Significance of Serum Biomarkers for Breast Cancer. Ўзбекистон Республикаси Санитария-эпидемиология ва жамоат саломатлиги хизмати илмий-амалий журнали , 3(3-4). извлечено от http://jurnal.sanepidrc.uz/index.php/sanepid/article/view/33*

11. *Mirzaeva M., Alimkhodjaeva L. RELATIONSHIP BETWEEN SERUM IL-6 AND TUMOR HISTOLOGICAL MANIFESTATIONS IN PREMENOPAUSAL BREAST CANCER PATIENTS WITH METABOLIC SYNDROME //Академические исследования в современной науке. – 2024. – Т. 3. – №. 40. – С. 43-45.*

12. *Munira Kh. Norbekova, Lola T. Alimkhodzhaeva, Sherzod I. Ruziyev, & Mohinabonu J. Khusanova. (2025). NAVIGATING DISTANCE METASTASES IN MULTIFOCAL BREAST CANCER. Central Asian Journal of Medicine, (3), 229-235. Retrieved from https://journals.tma.uz/index.php/cajm/article/view/1098*

13. *Rakha EA, El-Sayed ME, Lee AH, Elston CW, Grainge MJ, Hodi Z, et al. Prognostic significance of Nottingham histologic grade in invasive breast carcinoma. J Clin Oncol. 2008;26(19):3153–8. doi:10.1200/JCO.2007.15.5986.*

14. *Reis-Filho JS, Pusztai L. Gene expression profiling in breast cancer: classification, prognostication, and prediction. Lancet. 2011;378(9805):1812–23. doi:10.1016/S0140-6736(11)61539-0.*

14. *Reis-Filho JS, Pusztai L. Gene expression profiling in breast cancer: classification,*