PERIVASCULAR MAST CELLS AND ANGIOGENESIS IN THE TUMOR MICROENVIRONMENT OF SYNOVIAL SARCOMA

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Synovial sarcoma is characterized by marked histological and molecular heterogeneity, and angiogenesis as well as innate immune cells are considered potential sources of prognostic markers and therapeutic targets. This study aimed to evaluate the relationship between the quantitative and spatial characteristics of mast cells and angiogenesis in the tumor microenvironment of synovial sarcoma, as well as their prognostic significance. Using immunohistochemistry (tryptase/CD117, CD31/CD34, VEGF-A, α-SMA, CD3/CD8, CD68/CD163) and digital morphometry normalized to 1 mm^2, we analyzed 140 cases of synovial sarcoma. The intrathumoral, peritumoral, and perivascular (≤50 μm from CD31$^+$/CD34$^+$ vessels) zones, as well as the mastocyte degranulation index, were evaluated separately. Mast cells were detected in all observations; their density and signs of degranulation were greatest in the perivascular zone. Perivascular mast cells were positively correlated with both microvascular density and VEGF-A expression, and inversely correlated with α-SMA pericyte coverage; these relationships remained significant even after accounting for CD163$^+$ macrophages. A high microvascular density and increased perivascular mast cell counts were associated with an unfavorable survival prognosis, while pronounced CD8$^+$ infiltration predicted better outcomes. The developed integral Mast-Angio Score, which combines perivascular density, mast cell degranulation, microvascular density, and VEGF-A expression, improves the accuracy of prognostic stratification and can serve as a morphological basis for justifying combined antiangiogenic and immune therapy.

Keywords: mast cells, tryptase, angiogenesis, microvessel density, tumor microenvironment, synovial sarcoma, digital morphometry

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ПЕРИВАСКУЛЯРНЫЕ МАСТОЦИТЫ И АНГИОГЕНЕЗ В ОПУХОЛЕВОМ МИКРООКРУЖЕНИИ СИНОВИАЛЬНОЙ САРКОМЫ

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Синовиальная саркома характеризуется выраженной гистологической и молекулярной гетерогенностью, а ангиогенез и клетки врожденного иммунитета рассматривают как потенциальные источники прогностических маркеров и терапевтических мишеней. Целью исследования было оценить взаимосвязь количественных и пространственных характеристик мастоцитов с ангиогенезом в опухолевом микроокружении синовиальной саркомы и их прогностическую значимость. Проанализировано 140 случаев синовиальной саркомы с применением иммуногистохимии (триптаза/CD117, CD31/CD34, VEGF-A, α-SMA, CD3/CD8, CD68/CD163) и цифровой морфометрии с нормированием на 1 мм^2. Отдельно оценивали интратуморную, перитуморальную и периваскулярную (≤ 50 мкм от CD31$^+$/CD34$^+$ сосудов) зоны, а также индекс дегрануляции мастоцитов. Мастоциты выявлялись во всех наблюдениях, их плотность и признаки дегрануляции были максимальны в периваскулярной зоне. Периваскулярные мастоциты положительно коррелировали с микрососудистой плотностью и экспрессией VEGF-A и обратно — с перицитарным покрытием по α-SMA, эти связи сохранялись после учета CD163$^+$-макрофагов. Высокие значения микрососудистой плотности и периваскулярных мастоцитов ассоциировались с неблагоприятной выживаемостью, тогда как выраженный CD8$^+$-инфильтрат — с лучшими исходами. Разработанный интегральный Mast-Angio Score, объединяющий периваскулярную плотность и дегрануляцию мастоцитов, микрососудистую плотность и VEGF-A, повышает точность прогностической стратификации и может служить морфологической основой для обоснования комбинированной антиангиогенной и иммунной терапии.

Ключевые слова: тучные клетки, триптаза, ангиогенез, микрососудистая плотность, микроокружение, синовиальная саркома, цифровая морфометрия

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Synovial sarcoma (SS) accounts for 5–10% of soft tissue sarcomas. Its characteristic features include an aggressive clinical course, a high frequency of metastases, and a limited response to standard chemotherapy and immunotherapy. These facts justify the interest in studying the tumor microenvironment (TME), especially cells of innate immunity and angiogenesis, as potential sources of prognostic markers and therapeutic targets [1–3].

Mast cells are resident cells of the innate immune system; they contain granules with tryptase, chymase, histamine, cytokines, and growth factors. In tumor tissue, they can have both a pro-tumor effect, enhance angiogenesis, matrix remodeling, and immunosuppression via VEGF, tryptase, IL-8, and TNFb, and an antitumor effect, releasing TNFa, granzyme B, heparin, and mediators capable of inducing apoptosis of tumor cells or suppressing angiogenesis. There are two main phenotypes of mast cells: MCT (tryptase only) and MCTC (tryptase/chymase): their distribution and functional role depend on the type of tumor and the microenvironment [4–6].

The increased number of tryptase+ mast cells has been reported in various solid tumors, and it is known in such situations, the microvascular density (MVD) is often high; however, the role of the said mast cells in SS remains insufficiently studied. The data in literature are contradictory: on the one hand, mast cells are regarded as a source of proangiogenic factors; on the other hand, there are reports of their potential antitumor function and their association with a favorable prognosis in certain diseases. Most studies, however, lack a spatial assessment that factors in the localization of mast cells relative to blood vessels, although it is the perivascular zone that is key for angiogenesis and the delivery of nutrients to the tumor [4–9].

Another problem is methodological heterogeneity: researchers use different panels of immunohistochemical markers (tryptase, CD117), normalization methods (in the visual field or at 1 mm^2), rarely distinguish intra- and peritumoral zones, and almost never assess the perivascular density of mast cells or the degree of their degranulation. For SS, there are no standard criteria of quantitative and spatial assessment of mast cells aligned with angiogenesis (CD31/CD34, VEGF, MVD) and clinical prognostic data [10].

Taking into account the revealed role of mast cells as active regulators of the vascular niche and modulators of angiogenesis, this study aimed to give a comprehensive morphological description of these cells in the tissue of synovial sarcoma. We paid special attention to their quantitative and topographic parameters, including perivascular density and degree of degranulation, as well as the relationship with angiogenic features of the tumor microenvironment.

The purpose of this study was to evaluate the relationship between the quantitative and spatial characteristics of mast cells and angiogenesis in the tumor microenvironment of synovial sarcoma, and to determine their prognostic significance.

METHODS

The goal of this single-center retrospective study was to comprehensively describe morphometric characteristics of mast cells and angiogenic parameters in synovial sarcoma. The work included a standardized immunohistochemical assessment of mast cells (tryptase$^+$/CD117$^+$; density, perivascular localization, and degranulation index) and evaluation of vascular parameters (CD31/CD34, microvascular density, VEGF-A, and α-SMA), supplemented by digital morphometry normalized to the cut area (mm^2). The data for intra- and peritumoral zones (clinical and morphological characteristics, patient survival) were analyzed separately and then compared.

The study included 140 patients who were observed at the Pirogov Russian National Research Medical University. All of them had a morphologically confirmed synovial sarcoma (SS), which was the inclusion criterion. The cohort consisted of 74 men and 66 women; their age ranged from 4 to 84 years (median — 18.5 years). The materials used for the study were archival histological slides and paraffin blocks (FFPE). The cases considered included both first-time diagnoses and diagnostic reviews, provided that there was a sufficient volume of tumor tissue and enough clinical history data (age, gender, localization, size, stage, and treatment). Exclusion criteria: questionable diagnosis after revision, critically insufficient volume of tissue; repeated biopsy samples from the same lesion.

The factors and parameters assessed included the tumor's histological subtype (monophasic or biphasic), presence of necrosis, mitotic activity/Ki-67 index, stage, and metastatic status. There were two approaches to age stratification: ≤ 24 and ≥ 25 years, and < 18 and ≥ 18 years, which reflected the clinical and epidemiological features of SS.

For immunohistochemical study, we used the Leica Bond-III automatic stainer, Novocastra RTU antibodies (Leica Biosystems, UK), and Bond Polymer Refine (DAB) detection; Mayer hematoxylin was the counterstaining agent. For antigenic reprivelication, we used ER1 (pH 6.0) and/or ER2 (pH 9.0), as per IFU. The panel included tryptase and CD117 (mast cells), CD31 and CD34 (microvascular density), α-SMA (pericyte coverage), VEGF-A (angiogenic activity), CD3/CD8 (T cells), CD68/CD163 (macrophages). Additionally, we evaluated VEGFR2 (in the endothelium) and PDGFRa (in the stroma/perivascularly); the threshold of positivity was ≥ 10% of positive cells. H-score (0-300) was applied semi-quantitatively.

Scanned specimen normalized to 1 mm^2 were used for digital morphometry. Intra- and peritumoral zones were considered separately. Tissue within 50 μm of CD31$^+$/CD34$^+$ microvessels was defined as perivascular. Vessels with a lumen diameter >50 μm were excluded from the MVD calculation. To determine MVD, we used the Weidner hotspot method in fields of approximately 0.95 mm^2 and global WSI; additionally, we factored in the pericyte coverage by α-SMA.

Statistical analysis was performed in R 4.3.2. We used the Shapiro–Wilk test to assess the normality of distribution, the Mann–Whitney U or Kruskal–Wallis test for group comparisons, and Spearman's rank correlation test to evaluate relationships between variables. Spearman's partial correlation with CD163$^+$ control and multiple linear regression for MVD were used to account for the macrophage component. Multiple comparisons were adjusted using the Benjamini–Hochberg false discovery rate (FDR) procedure. Survival outcomes (MFS and OS) were evaluated using the Kaplan–Meier and Cox regression methods. The threshold of statistical significance was $p < 0.05$.

RESULTS

Immunohistochemical and morphometric studies were performed for all 140 cases. The immune infiltrate of SS had the "restrained-cold" TME profile: a low density of CD3$^+$/CD8$^+$-T-lymphocytes and a pronounced predominance of CD68$^+$/CD163$^+$ macrophages, which is consistent with the literature data on sarcomas. There were no significant differences in microvascular density (MVD) between monophasic and biphasic variants [11, 12].

Morphological analysis of the CD31-positive vascular bed showed clear zonal differences. A dense network of thin-walled capillaries with branching and looping contours,

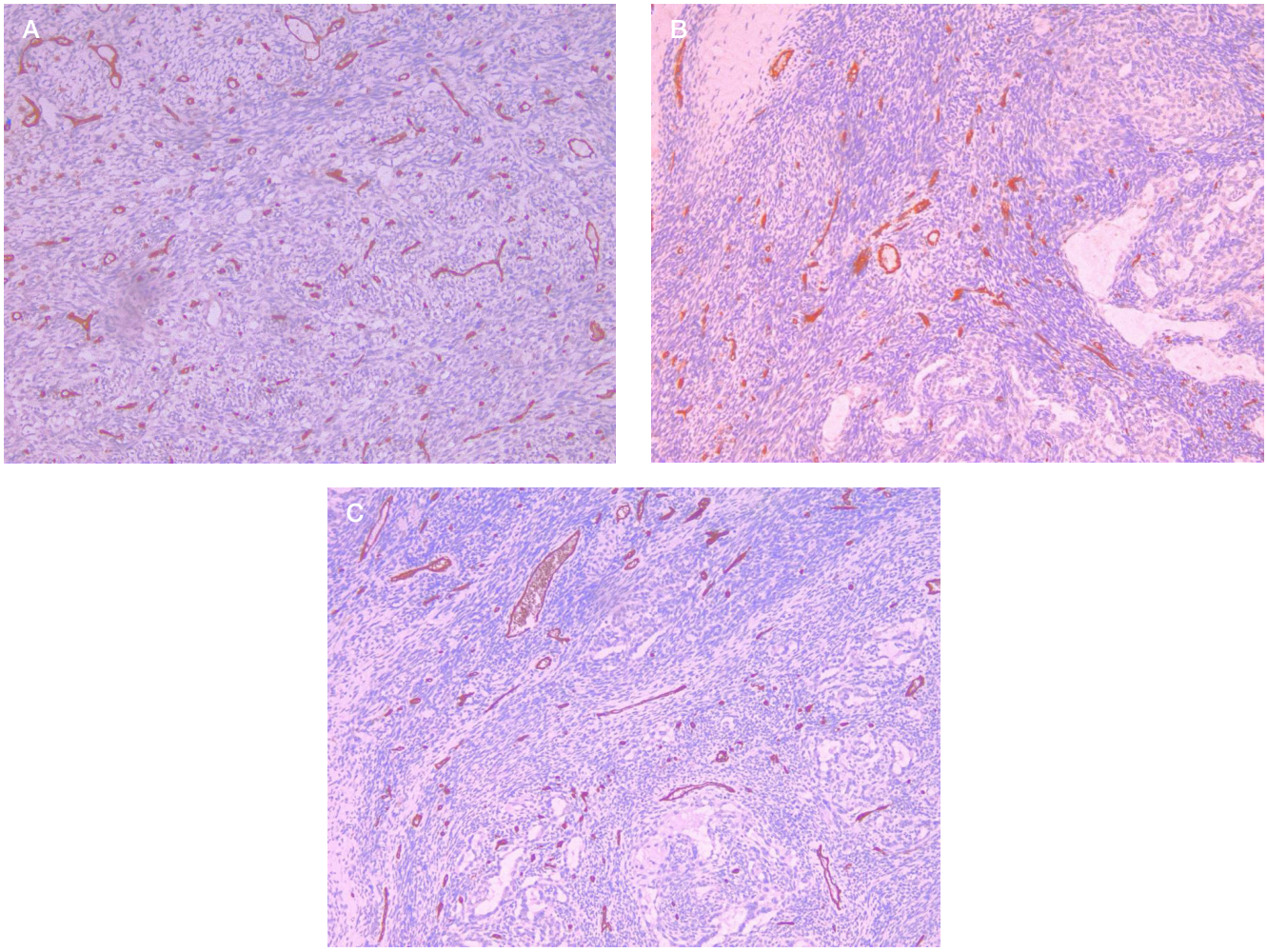

Fig. 1. A. Intratumoral zone (CD31, ×200). A dense network of thin-walled capillaries with branching and looping contours, peculiar to the hotspots of angiogenesis. **B**. Peritumoral zone (CD31, ×200). An ordered vascular network of lower density, vessels oriented along the collagen bundles. **C**. Peritumoral zone (CD31, ×200). Mosaic microvascular proliferation composed of small and medium vessels, reflecting the spatial heterogeneity of angiogenesis

corresponding to the "hot" spots of angiogenesis, was formed in the intratumoral areas. The endothelium was uniformly positive for CD31, with no signs of atypia, which reflects active sprouting angiogenesis. In the peritumoral stroma, the vascular network looked more orderly, with lower density and orientation along the collagen bundles. Near the invasive front, there was a mosaic microvascular proliferation composed of small and medium vessels, confirming the spatial heterogeneity of angiogenesis. These features are shown in Fig. 1 A, B, and Fig. 2 presents their quantitative differences; the median MVD in the intratumoral zone was ~110 vessels/mm^2, that in the peritumoral zone — about 80-90 vessels/mm^2.

CD34 staining revealed similar trends, but with expected higher values (intratumoral median ~127 vessels/mm^2, peritumoral median ~95 vessels/mm^2), which is associated with a wider marking of endothelial profiles. Thus, CD31 predominantly shows active angiogenic spots, whereas CD34 reveals the combination of mature and immature vessels.

Mast cells (MC) were visualized as CD117$^+$ elements, mostly oval in shape, with clear membrane and cytoplasmic positivity. Their distribution was governed by the topography: in the perivascular zone (≤ 50 μm from CD31$^+$/CD34$^+$ vessels), the density of MC was highest, reaching a median of ~154 cells/mm^2, while in the intratumoral areas it was about 93 cells/mm^2; the peritumoral zone had ~144 cells/mm^2, a value between the two above. From the viewpoint of spatial concentration of MC, there were detected signs of partial degranulation — extracellular granules along the cell periphery, indicating functional activity. In the intratumoral parenchyma, MCs were mainly single, not oriented along the vessels. Fig. 3 A, B present these observations, and Fig. 4 gives shows the quantitative comparison.

The analysis of angiogenic markers showed a moderately high expression of VEGF-A (H-score ~150 [100–220]) and partial vascular pericyte coverage by α-SMA (~25%), which indicates predominance of morphologically immature vessels. Expression of VEGFR2 and PDGFRa receptors was observed

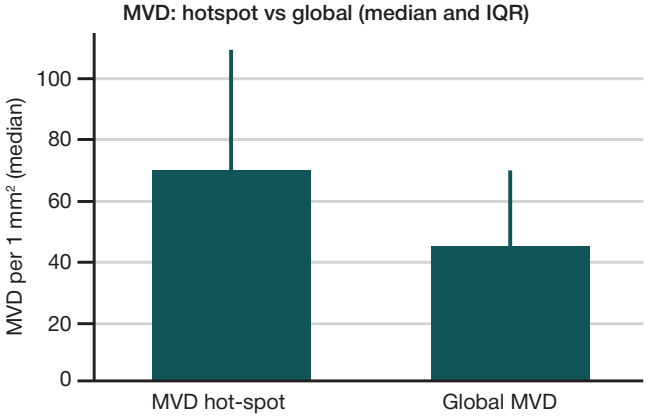

Fig. 2. Microvascular density (MVD, CD31): comparison of Weidner hotspots and whole-section assessment

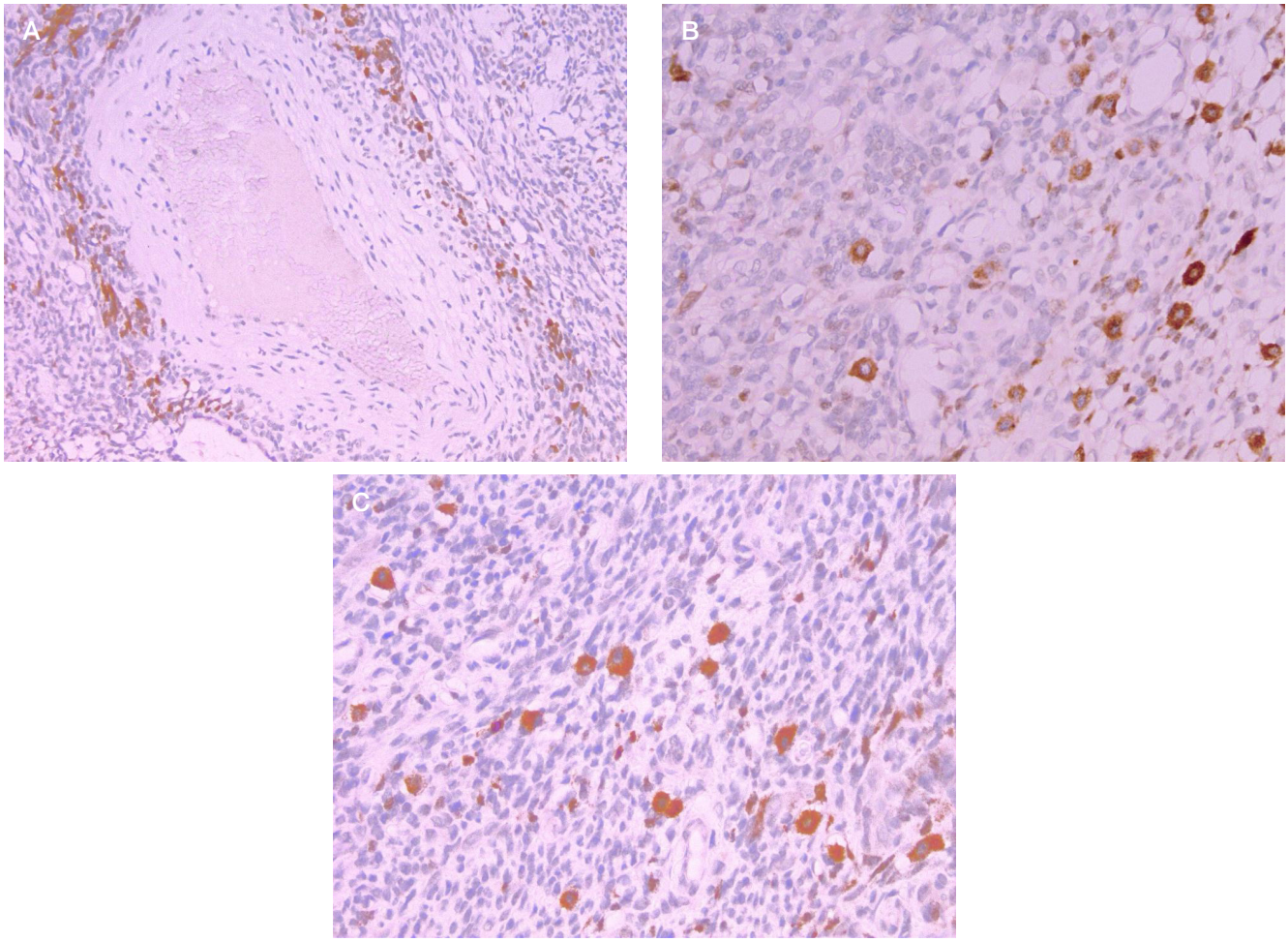

Fig. 3. A. Perivascular zone ≤ 50 μm (CD117, ×200). Clustering of mast cells along the vascular wall; individual cells with extracellular granules (an indirect sign of degranulation). **B**. Perivascular zone ≤ 50 μm (CD117, ×400). Clusters of mature granular mast cells forming vascular cuffing. **C**. Intratumoral zone (CD117, ×400). Solitary mast cells lacking pronounced perivascular orientation, with partial loss of granularity

in 20% and 46–70% of cases, respectively, which confirms the involvement of both signaling axes in the regulation of angiogenesis in synovial sarcoma (Fig. 5 A, B).

Correlation analysis (Fig. 6) confirmed a strong link between mast cell activity and angiogenesis: perivascular MC density positively correlated with MVD in hotspots (R_s = 0.70) and globally (r_s = 0.62), as well as with VEGF-A (r_s = 0.40), and degranulation index — with MVD (r_s = 0.55). These dependencies persisted after adjustment for CD163⁺ macrophages, which confirms independent contribution of mast cells to angiogenesis. The inverse correlation of MVD with α-SMA pericyte coverage (R_s = –0.35) points to the predominance of immature vessels in the zones of mastocytic activity.

Considering the sample though the lens of age (≤ 24 and ≥ 25 years old; < 18 and ≥ 18 years old), we failed to identify significant differences in MVD, VEGF-A, and MC density ($p > 0.05$), which means age is not a factor modifying angiogenic profile. In the subgroup for which we had the survival data, increased value of MVD and perivascular MC amount were associated with less favorable outcomes, while a high density of CD8⁺ T lymphocytes usually meant better MFS/OS.

An integral Mast–Angio Score was developed based on these parameters. It includes perivascular density of MC, MVD, VEGF-A, and degranulation index. Internal validation showed an improvement in the c-index and NRI/IDI indicators compared to traditional clinical and morphological models, which confirms the prognostic significance of mastocyte-angiogenic metrics in SS [13–15].

DISCUSSION

The obtained morphological and quantitative data confirm active angiogenesis and close vascular-immune interaction in the microenvironment of SS. The increased intratumoral CD31 and CD34 MVD reflects the predominance of sprouting angiogenesis in the tumor parenchyma, whereas the vascular network in the peritumoral stroma is less dense and more structured. The difference between the markers is explained by differences in their specificity: CD31 predominantly shows

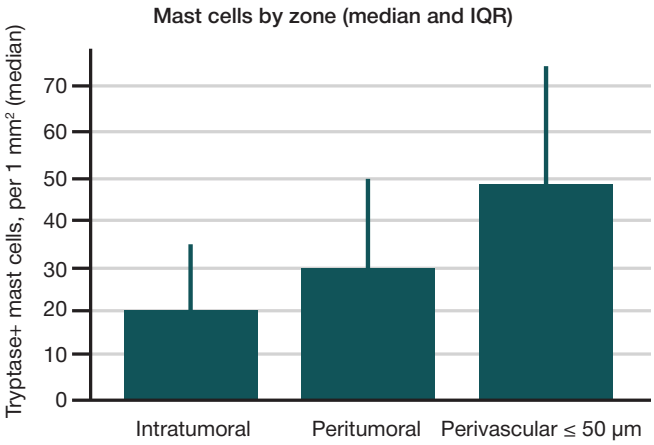

Fig. 4. The density of tryptase+ mast cells in the intratumoral, peritumoral, and perivascular (≤ 50 μm from CD31⁺/CD34⁺ vessels) zones

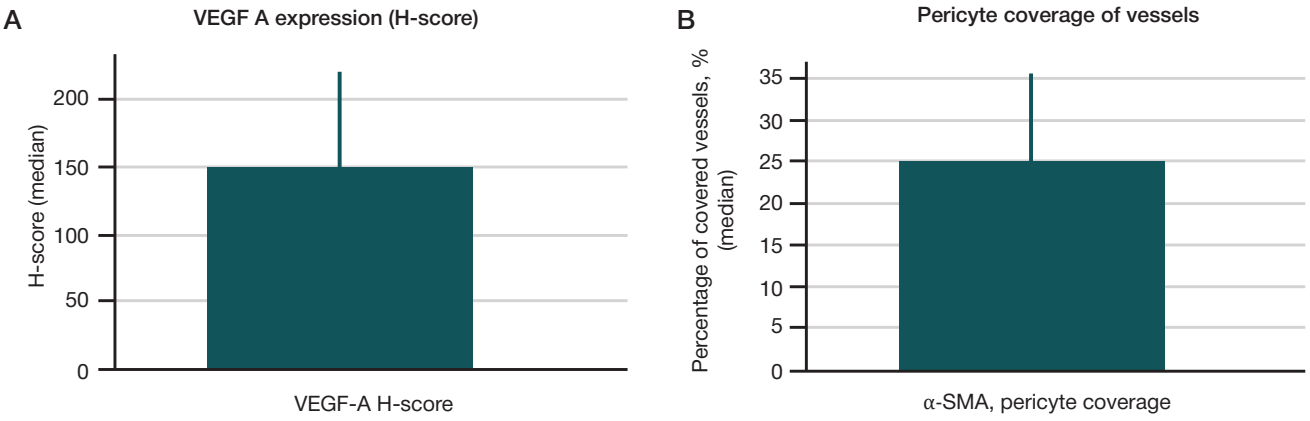

Fig. 5. A. VEGF-A expression (H-score) in synovial saracoma tissues. **B**. Pericyte coverage of vessels, α-SMA.

a functioning endothelium, while CD34 additionally reveals immature endothelial structures. Therefore, CD31 should be used as a basic marker for interzonal comparisons, and CD34 as a sensitive indicator of an expanded range of vascular structures.

A key observation is a pronounced perivascular accumulation of CD117⁺ mast cells in the zone ≤ 50 μm from microvessels with a relatively lower density in the intratumoral parenchyma. This pattern aligns with the known ability of mast cells to produce angiogenic mediators — tryptase, histamine, VEGF-A, FGF-2, proteases, and chemokines that mediate extracellular matrix remodeling and increase vascular permeability. This spatial convergence of MC with microvessels enables paracrine effects on the endothelium and pericytes, which enhance growth and stabilization of the newly formed vessels. Similar mechanisms have been described in Ewing's sarcoma and osteosarcoma, where mast cell density positively correlates with MVD and VEGF expression.

The observed correlations between the perivascular density of MC, MVD, and VEGF-A levels confirm the involvement of mast cells in the regulation of angiogenesis. The inverse correlation between MVD and α-SMA pericyte coverage points to the predominance of morphologically immature vessels in the areas of active angiogenesis. The independence of these associations from the density of CD163⁺ macrophages highlights the independence of contribution of mast cells to angiogenic processes.

The results of this study are consistent with the modern concepts of spatial organization of sarcoma cellular ecosystems, where angiogenic and immune niches form interconnected microenvironments that affect the prognosis [16]. Our data clarify one of the aspects of this model — the role of mast cells as active elements of the vascular niche. The described perivascular concentration of MCs and their degranulation confirm the tissue heterogeneity of mast cells and their involvement in the recruitment of other cells of innate immunity [17].

The revealed pattern is clinically significant because high MVD in combination with perivascular accumulation of MC forms the angiogenic phenotype of the tumor microenvironment that is associated with an unfavorable course. Such vascular-immune profiles are considered a potential target for complex treatment strategies combining antiangiogenic drugs with immunotherapy [18]. This is consistent with the concept of mast cells as mediators that modulate the antitumor immune response, and with data suggesting their potential therapeutic involvement when checkpoint inhibitors are used. [19, 20].

Thus, our results expand current understanding of vascular–immune interactions in synovial sarcoma and highlight the key role of perivascular mast cells in promoting the angiogenic phenotype of the tumor microenvironment, as well as their potential as therapeutic targets.

CONCLUSIONS

In synovial sarcoma, perivascular mast cells form a reproducible topographic pattern with the highest density in the zone ≤ 50 μm from CD31⁺/CD34⁺ microvessels and a higher degree of degranulation compared to parenchyma. Their accumulation is associated with the angiogenic TME phenotype: we revealed a positive correlation with MVD (both in hotspots and globally)

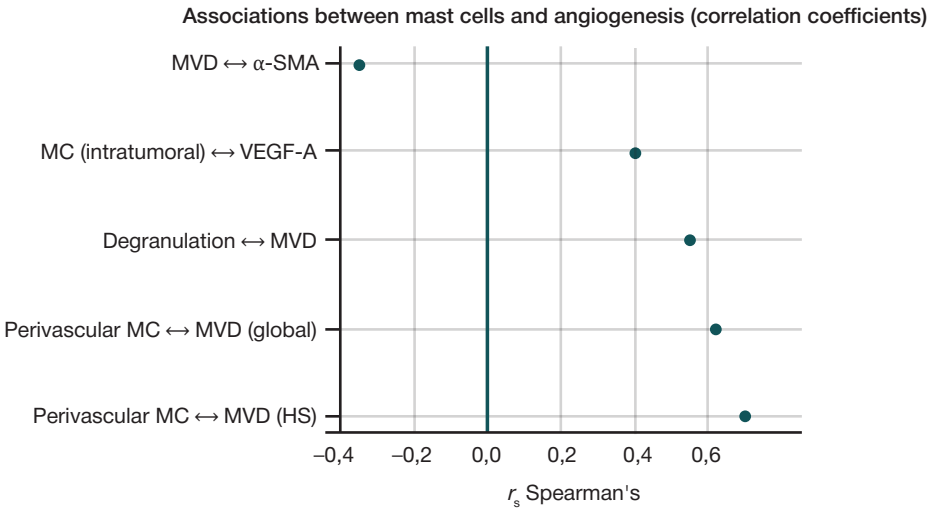

Fig. 6. Correlations between mast cell density, MVD, VEGF-A and α-SMA pericyte coverage (Spearman's coefficients)

and VEGF-A expression, and a simultaneous negative association with with α-SMA pericyte coverage, which points to the predominance of morphologically immature vessels. These dependencies persist after adjustment for $CD163^+$ macrophages, confirming the independent contribution of mast cells to the vascular niche. As for age, the respective analysis revealed that it does affect the mast cell angiogenic metrics significantly. In the subgroup with survival data, higher MVD and perivascular mast cell density were associated with worse outcomes, while pronounced $CD8^+$ infiltration meant better outcomes. The proposed integral Mast-Angio Score, which combines perivascular density and mast cell degranulation, MVD, and VEGF-A, increased the discriminative ability of the prognostic model (c-index growth, NRI/IDI improvement) in terms of the standard clinical and morphological features. Archived histological slides and FFPE blocks can be used in a standard IHC test aimed at learning the values of these parameters; it can be integrated into a synoptic report as an additional layer in risk stratification. The results of this study provide a rationale for clinical trials of complex approaches — antiangiogenic therapy combined with modulation of effector functions of mast cells and/or immunotherapy — in carefully selected subgroups of patients with an angiogenically active profile.

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