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ORIGINAL ARTICLE

Relationship Between Mast Cell Density and Various Histological Features in Melanocytic Lesions

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Abstract

Background/Aim: Mast cells, derived from multipotent haematopoietic progenitors in the bone marrow, are immune cells typically found in varying concentrations within melanocytic lesions. Aim of this study was to investigate mast cell density (MCD) in 182 melanocytic lesions, with a particular focus on its association with demographic and histopathological characteristics.

Methods: MCD and secondary changes in melanocytic lesions were assessed histopathologically using paraffin-embedded tissue samples analysed under a Nikon Eclipse E400 microscope.

Results: MCD was significantly higher in lesions from females compared to males and in lesions located on the head and neck compared to those on the arm, trunk and leg. Nevi exhibited higher MCD than melanomas, with marked differences observed among specific lesion types. Histopathological analysis revealed that lesions devoid of clear cells and those exhibiting an angioadnexocentric pattern had significantly elevated MCDs. Furthermore, lesions characterised by prominent elastic fibres, mucin deposition and certain adjacent structural interactions demonstrated increased MCDs.

Conclusion: These findings underscore the complexity of mast cell functions in melanocytic lesions, offering valuable insights that may enhance diagnostic and therapeutic strategies.

Key words: Mast cells; Melanocytic lesions; Nevus, pigmented; Skin; Secondary lesions.

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Introduction

Mast cells, derived from multipotent haematopoietic progenitors in the bone marrow, are immune cells typically found in varying concentrations within melanocytic lesions. Their presence can influence the remodelling of the lesion's microenvironment, making the determination of these relationships a significant research challenge. Several studies have confirmed the role of mast cells in tumour growth and the progression of various human neoplasms, including melanoma and nevi. For instance, Kaszuba et al[1] reported an elevated risk of melanoma and non-melanoma skin cancers in patients with mastocytosis compared to the general population. Additionally, Ribatti et al and Segura-Villalobos et al[2, 3] have demonstrated that mast cells are involved in tumour progression and immune modulation in skin cancers.

Moreover, other research has identified a correlation between mast cell density (MCD) and mela-

noma aggressiveness, as well as poorer patient outcomes. Siiskonen et al[4] found that lower MCD is negatively correlated with survival in melanoma patients. Given the variability of MCD in nevi and melanomas, authors generally link these findings to the carcinogenesis pathway.[5, 6]

One of the challenges in studying mast cells in tumorigenesis is the inherent heterogeneity of mast cell populations and their diverse functional states within the tumour microenvironment. Some literature suggests that mast cells can release angiogenic factors that may promote tumour growth, while other studies indicate that they may exert protective effects.[7-10] This complexity complicates the interpretation of mast cell data and underscores the necessity for further investigation.

This study aimed to explore the relationship between MCD, demographic features of patients and various secondary changes present in melanocytic lesions. It was anticipated that the findings will enhance understanding of mast cells and their potential utility in routine diagnostic practices.

Methods

This study included all paraffin-embedded tissue samples from patients diagnosed with melanocytic lesions (both benign and malignant) at Clinical Hospital Shtip, North Macedonia, over a five-year period (2019-2023), totalling 182 samples.

Inclusion criteria: patients with histologically confirmed melanocytic lesions, availability of formalin-fixed, paraffin-embedded tissue suitable for histopathological analysis, lesions with sufficient tissue quality for mast cell density assessment under light microscopy, cases with complete demographic data, lesions exhibiting secondary changes.

Exclusion criteria: poorly preserved or degraded tissue samples unsuitable for microscopic evaluation, lesions lacking clear histopathological classification, cases with incomplete demographic or clinical data, prior treatment (eg, excision, laser therapy) that may alter mast cell density or tissue architecture.

The diagnoses were reviewed by three pathologists and a dermatopathologist. Archived demographic data of the patients, including age, gender and lesion localisation, were incorporated into the analysis alongside data on secondary changes in the melanocytic lesions.

The secondary changes in the melanocytic lesions were categorised into five primary groups,[11, 12] subdivided into specific categories:

1. Cytological changes (CC): This category included alterations such as nevus with clear cell cytoplasm, oncocytic transformations, granular cell changes and eosinophilic cytoplasmic inclusion bodies.
2. Architectural changes (A): This group encompassed pseudogranulomatous changes, plexiform arrangements and angioadnexocentric patterns.
3. Changes in extracellular matrix (CEM): This included the prominence of elastic fibres, *osteonevus* of Nanta and mucin deposition.
4. Changes imitating non-melanocytic components (CINC): This category covered *pseudolacunae*/Pseudo-Dabska arrangements, neurotisation (whether c-cell type or pseudomeissnerian type), lipidation, angiomatoid arrangements and structures resembling tubular formations.
5. Interactions with adjacent structures (IAS): This group includes interactions with the epidermis (IAS-E), conditions such as folliculitis (IAS-F) and the formation of epidermal, dermal, or trichilemmal cysts (IAS-T).

Histopathological analysis

Histological and cytological examinations were conducted on tissue specimens fixed in 10 % formalin and embedded in paraffin, resulting in sections of 5 µm thickness. These sections were stained using standard haematoxylin and eosin (HE) methods.

Histochemical analysis of stromal mucin using alcian blue - PAS staining

A 4 µm thick section of selected tissue, fixed in formalin and embedded in paraffin, was prepared for histochemistry. The sections were deparaffinised and hydrated to distilled water and then immersed in Alcian blue solution for 5 minutes after what running under tap water for 3 minutes was performed, followed by rinsing with distilled water. The slides then were immersed in periodic acid solution for 10 minutes after what

were placed under running tap water for 3 minutes, followed by rinsing with distilled water. Immersion in Schiff's reagent for 15 minutes was next step after what were placed under running tap water for 3 minutes, followed by rinsing with distilled water. The slides were immersed in haematoxylin solution modified according to Gill III for 20 seconds and then placed under running tap water for 3 minutes. Dehydration through an ascending series of alcohols was done and after immersion in xylene, the slides were mounted in Entellan™. Mucous substances were visualised as light blue substances in the stroma of the lesions.

Histochemical analysis for visualisation of elastic fibres – elastica van Gieson

Single sections 4 µm thick from selected tissue, fixed in formalin and embedded in paraffin, were conventionally deparaffinised and rehydrated. After reagents preparation, slides with the section were immersed in Elastin acc. to Weigert-resorcin fuchsin solution for 10 minutes and then rinsed under running water for 1 minute. Immersion in Weigert's iron haematoxylin staining solution for 5 minutes, was next step, followed by rinsing under tap water for 1 minute. Immersion in Pirofuchsin solution according to van Gieson for 2 minutes, was performed. Dehydration through an ascending series of alcohols was done and after immersion in xylene, the slides were mounted in Entellan™. Elastic fibres were visualised as black coloured fibres in the stroma.

Histochemical analysis Giemsa (May-Grunwald) procedure for mast cells

Giemsa (May-Grunwald) procedure for mast cells was conducted as it follows: deparaffinised and hydrated 4 µm thick sections were placed in staining tray and flood with Working May-Grunwald Solution for 6 minutes, with occasionally agitating. Slides were flooded with phosphate buffer solution (PBS), pH 6.8 until no stain runs off. Then flooding slides with working Giemsa solution for 13 minutes, was conducted with occasionally agitating. Slides than were flood with PBS until no stain runs off. Differentiation was made by dipping slides in acetic acid solution (0.25 %). Dipping slides 20 times in PBS, followed by quickly dipping in distilled water and air drying at room temperature. Last step was dipping slides in xylene or xylene substitute and mounted in Entellan™. Mast cells were visualised as oval to elongated cells, with dark blue nuclei and purple to red cytoplasmatic granules (Figure 1: A, B, C).

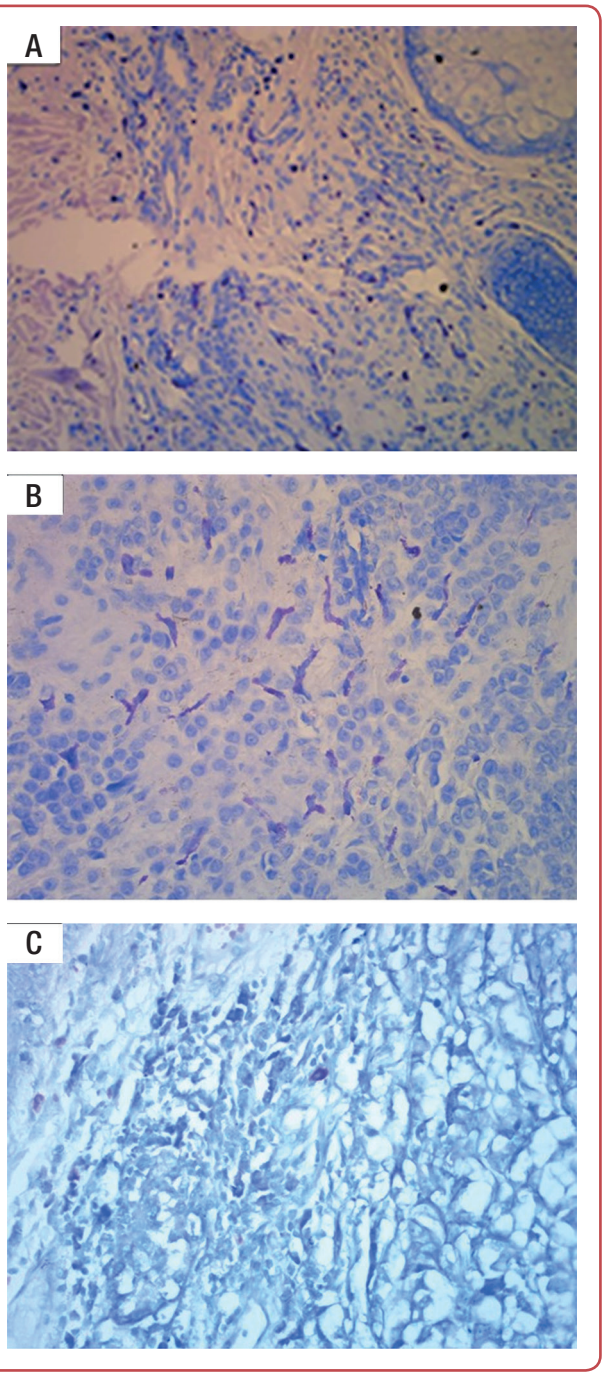

Figure 1: A and B – Mast cells in melanocytic nevi which exhibited prominent elastic fibres at the base and intratumorally: A - Giemsa stain x20; B – Giemsa stain x40; C– Mast cell in melanoma with clear cells – Giemsa stain x40

Mast cells counting

The counting of positive mast cells was performed using a modified hotspot counting technique, as described in previous studies on cell quantification. Initially, slides were scanned at low magnification (×40 to ×100) to identify the densest area of mast cells within the tumoral stroma. Once the hotspot was located, individual positively stained

mast cells were counted at high power (400 magnification), which represented the area with the highest concentration of mast cells in the tissue sample. All analyses were conducted using the same microscope and the results were documented photographically.

Considering the microscope magnification (×400) and a field diameter of 0.05 mm, it was calculated the field area to be 0.24 mm^2, which was subsequently used to express mast cell density per mm^2.[13]

Statistical analysis

Statistical analyses were performed using XLSTAT software with a 95 % confidence level. Non-parametric methods were employed due to the non-normal distribution of the collected data. The Kruskal-Wallis test and the Mann-Whitney U-test were utilised for continuous data comparisons. Additionally, correlations between variables were assessed and expressed through the Spearman correlation coefficient (ρ) and its coefficient of determination (ρ^2). All tested results were significant when $p < 0.05$.

Results

Table 1 presents descriptive statistics for MCD in 182 melanocytic lesions categorised by age, gender, lesion type and lesion location. The results of the Mann-Whitney U test indicated that MCDs in lesions from younger patients (< 50 years) were significantly higher than those from patients

Table 1: Descriptive statistics of mast cell densities grouped in 5 categories together with results of testing differences between subcategories and Spearman coefficient of correlation (ρ)

Category	Subcategory	N (%)	Mast cell density (1/mm^2)			p*	p**
			25-75 %	Median	Mean ± SD		
Age (years)	< 50	111 (61.0 %)	12.5 - 70.8	25.0	51.1 ± 58.9	0.0003	0.0003
	≥ 50	71 (39.0 %)	4.2 - 45.8	8.3	38.6 ± 69.3		
Gender	Female	126 (69.2 %)	8.3 - 70.8	25.0	53.4 ± 65.9	0.0002	-0.2800
	Male	56 (30.8 %)	4.2 - 33.3	8.3	30.1 ± 53.9		
Melanocytic lesion's location	Head and neck	65 (35.7 %)	12.5 - 125.0	33.3	71.6 ± 84.4	< 0.0001	-0.3100
	Arm	8 (4.4 %)	0.0 - 25.0	8.3	21.9 ± 32.3		
	Trunk	71 (39.0 %)	4.2 - 33.3	12.5	29.9 ± 41.2		
	Leg	11 (6.0 %)	4.2 - 6.3	4.2	8.7 ± 14.1		
	Unknown	27 (14.8 %)	12.5 - 79.2	45.8	50.5 ± 47.3		
Type of melanocytic lesions	Nevus	140 (76.9 %)	12.5 - 80.2	29.2	57.5 ± 67.6	< 0.0001	-0.5200
	Melanoma	42 (23.1 %)	0.0 - 8.3	4.2	8.7 ± 16.7		
Type of melanocytic lesions (2)	EDN	13 (7.1 %)	4.2 - 133.3	62.5	76.9 ± 74.7	< 0.0001	-0.5000
	IDN	117 (64.3 %)	12.5 - 79.2	29.2	59.0 ± 68.4		
	DN	10 (5.5 %)	4.2 - 12.5	6.3	14.6 ± 16.8		
	SSM	2 (1.1 %)	6.3 - 18.8	12.5	12.5 ± 17.7		
	UM	17 (9.3 %)	0.0 - 8.3	4.2	9.3 ± 20.9		
	LMM	4 (2.2 %)	0.0 - 5.2	2.1	3.1 ± 4.0		
	NM	19 (10.4 %)	0.0 - 8.3	4.2	9.0 ± 14.7		
Total		**182 (100.0 %)**	**4.2 - 62.5**	**16.7**	**46.2 ± 63.2**		

p- results of testing differences in MSD between subcategories; ρ **-Spearman coefficient of correlation between MSD and category; N: Nevus; M: Melanoma; EDN: Epidermal-dermal melanocytic nevi / compound nevus; IDN: Intradermal melanocytic nevi; DN: Dysplastic nevus; SSM - Superficial spreading melanoma; UM: Invasive melanoma - not otherwise specified/unspecified; LMM: Invasive melanoma -lentigo malignant melanoma; NM: invasive melanoma - nodular type;*

aged 50 years and older (MW, p = 0.0003). Additionally, lesions from female patients exhibited higher MCDs compared to those from male patients (MW, p = 0.0002). As anticipated, MCDs were also higher in lesions located on the head and neck compared to those on the arm, trunk and leg (MW, p < 0.0001).

Furthermore, differences in MCD among various types of melanocytic lesions were examined. MCDs in nevi were generally higher than in melanomas for all lesion types, with the exception of dysplastic nevi (DN), where MCDs were comparable to those in melanomas (p < 0.0001).

Next, potential relationships between secondary changes in the lesions and MCD was investigated. Analysis revealed that MCDs were significantly higher in lesions lacking clear cells (CC = 0) compared to those containing clear cells (CC = 1) (p = 0.0018; Table 2). Additionally, lesions exhibiting an angioadnexocentric pattern (AA = 1) had higher MCDs than those without this feature (AA = 0, p < 0.0001; Table 2). Lesions with prominent elastic fibres at the base (CEM-BL = 1) also showed significantly higher MCDs compared to those without this characteristic (CEM-BL = 0, p < 0.0001; Table 2). Similarly, lesions containing elastic fibres between tumour cells (CEM-TL = 1)

Table 2: Descriptive statistic of mast cell densities grouped according to histopathological and architectural features together with results of testing differences between subcategories (p) and Spearman coefficient of correlation (ρ)

Category	Subcategory	N (%)	Mast cell density (1/mm²)			p*	p**
			25-75 %	Median	Mean ± SD		
CC	0	156 (61.0 %)	8.3 - 67.7	16.7	49.7 ± 65.8	0.0018	-0.23
	1	26 (14.3 %)	0.0 - 29.2	4.2	25.2 ± 40.1		
AA	0	105 (57.7 %)	4.2 - 45.8	12.5	31.0 ± 46.4	< 0.0001	0.29
	1	77 (42.3 %)	12.5 - 91.7	33.3	66.9 ± 76.3		
CEM – BL	0	28 (15.4 %)	4.2 - 12.5	4.2	12.9 ± 19.2	< 0.0001	0.30
	1	154 (84.6 %)	8.3 - 70.8	25.0	52.3 ± 66.5		
CEM – TL	0	53 (29.1 %)	4.2 - 16.7	4.2	17.2 ± 26.4	< 0.0001	0.36
	1	129 (70.9 %)	8.3 - 83.3	29.2	58.1 ± 69.9		
CEM-S	0	51 (28.0 %)	0.0 - 16.7	8.3	15.0 ± 23.3	< 0.0001	0.39
	1	131 (72.0 %)	8.3 - 83.3	29.2	58.4 ± 69.5		
CINC-PL	0	116 (63.7 %)	4.2 - 42.7	12.5	41.0 ± 65.8	0.0071	0.20
	1	66 (36.3 %)	12.5 - 77.1	31.3	55.4 ± 57.9		
CINC – CN	0	84 (46.2 %)	4.2 - 16.7	8.3	20.9 ± 42.7	< 0.0001	0.52
	1	98 (53.8 %)	12.5 - 89.6	43.8	67.9 ± 69.8		
CINC – PM	0	154 (84.6 %)	4.2 - 45.8	12.5	37.4 ± 53.0	< 0.0001	0.32
	1	28 (15.4 %)	32.3 - 134.4	64.6	94.5 ± 89.6		
CINC – L	0	158 (86.8 %)	4.2 - 45.8	12.5	36.2 ± 50.8	< 0.0001	0.37
	1	24 (13.2 %)	38.5 - 163.5	83.3	112.2 ± 92.9		
CINC -T	0	152 (83.5 %)	4.2 - 59.4	16.7	43.1 ± 61.3	0.0545	0.14
	1	30 (16.5 %)	9.4 - 88.5	29.2	61.8 ± 71.4		
IAS-F	0	144 (79.1 %)	4.2 - 59.4	16.7	42.5 ± 57.5	0.5746	0.04
	1	38 (20.9 %)	8.3 - 77.1	20.8	60.3 ± 80.8		
IAS-T	0	172 (94.5 %)	4.2 - 63.5	16.7	46.3 ± 63.6	0.7519	0.02
	1	10 (5.5 %)	8.3 - 53.1	25.0	45.0 ± 59.1		
IAS-E	0	108 (59.3 %)	4.2 - 30.2	12.5	32.9 ± 55.6	< 0.0001	0.36
	1	74 (40.7 %)	12.5 - 83.3	45.8	65.6 ± 68.9		

p- results of testing differences in MSD between subcategories. The test is significant when p < 0.05; ro**-Spearman coefficient of correlation between MSD and category. CC: Clear cells; AA: Angioadnexocentric pattern; CEM-BL: CEM – prominence of elastic fibres at the base of a lesion; CEM-TL: CEM – prominence of elastic fibres between tumour cells of a lesion; CEM-S: CEM – intratumoral stroma mucin deposition; CINC-PL: CINC – pseudolacune; CINC-CN: CINC – C-cell type neurotisation; CINC-PM: CINC – pseudomeissnerian ; CINC-L: CINC – lipidation; CINC-T: CINC -tubular; IAS-F: IAS-F-folliculitis; IAS-T: IAS-T - trichilemmal/epidermal cyst; IAS-E: IAS-E – seborrheic keratosis like change;*

had significantly higher MCDs than those without such fibres (CEM-TL = 0, $p < 0.00001$; Table 2). The accumulation of mast cells in lesions with intratumoral stromal mucin deposition (CEM-S = 1) was also significantly greater than in lesions without mucin deposition (CEM-S = 0, $p < 0.0001$; Table 2).

Finally, the interaction of lesions with adjacent structures was further evaluated, revealing significant associations. Lesions exhibiting *pseudolacunae* (CINC-PL; Table 2), C-cell type neurotisation (CINC-CN; Table 2), pseudomeissnerian type neurotisation (CINC-PM; Table 2), lipidation (CINC-L; Table 2) and tubular patterns (CINC-T; Table 2) consistently demonstrated significantly higher mast cell densities compared to lesions lacking these changes ($p < 0.05$; Table 2).

Additionally, the relationship between the interaction of melanocytic lesions with neighbouring structures and MCD was examined. The relationships between MCD and lesions with and without IAS-F (folliculitis) and IAS-T (trichilemmal/epidermal cyst) were not found to be significant (Table 2). Conversely, lesions exhibiting IAS-E (seborrheic keratosis-like changes) demonstrated significantly higher MCDs compared to those without this feature ($p < 0.0001$; Table 2).

To quantify the univariable contributions of each category to variations in MCD Spearman coefficients of determination was calculated, with the results presented in Figure 2.

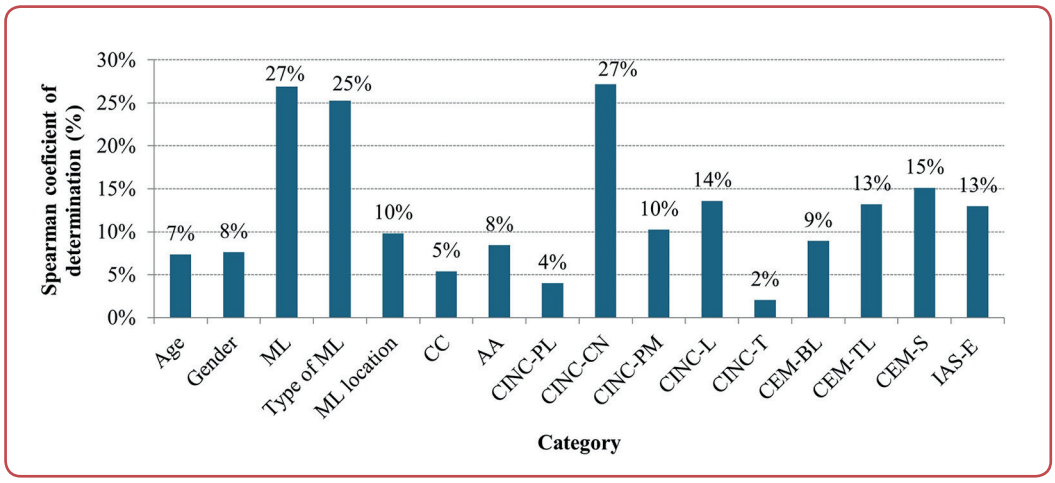

Figure 2: Spearman coefficient of determination (ρ^2) for mast cell densities and significantly corelated categories

CC: Clear cells; AA: Angioadnexocentric pattern; CINC-PL: CINC – pseudolacune; CINC-CN: CINC – C-cell type neurotisation; CINC-PM: CINC – pseudomeissnerian ; CINC-L: CINC – lipidisation; CINC-T: CINC -tubular ; CEM-BL: CEM – prominence of elastic fibres at the base of a lesion; CEM-TL: CEM – prominence of elastic fibres between tumour cells of a lesion; CEM-S: CEM – intratumoral stroma mucin deposition; IAS-E: IAS-E – seborrheic keratosis like change;

Discussion

The study evaluates MCD values in 182 melanocytic lesions, reporting a median concentration of 16.7 [quartiles: 46.2 - 63.2] (Table 1). The observed values exhibited high variability, which may reflect the complex roles of mast cells in melanocytic lesions.

Presented analysis indicates a negative correlation between MCD and patient age, gender and lesion location. Higher MCD was associated with younger patients and females compared to older and male patients. This suggests that MCD may be influenced by hormonal factors or age-related changes in the immune system, which can affect mast cell production and function, as well as cumulative UV radiation exposure. Similar findings have been reported in other studies, indicating that cellular aging contributes to a reduction in MCD over time.[14-16]

MCD was significantly lower in melanomas compared to nevi, suggesting distinct roles for mast cells in benign versus malignant lesions. Specifically, epidermal and intradermal nevi exhibited

higher MCD compared to dysplastic nevi (DN), unspecified melanomas (UM), *lentigo maligna melanomas* (LMM) and nodular melanomas (NM) ($p < 0.05$). These observations are consistent with findings by Siiskonen et al,[4] suggesting that serine proteases from mast cells may have a protective role in the pathogenesis of melanoma.

Furthermore, Damsky and Bosenberg[17] highlighted the complex relationship between nevi and melanoma, reviewing epigenetic changes in melanoma and nevus tissues. This indirectly suggests that the tumour microenvironment, including mast cell presence, may influence tumour behaviour through epigenetic modifications. In general, higher MCD in nevi may indicate a protective role against malignant transformation, whereas a decreased presence of mast cells in melanoma could correlate with tumour progression and poorer outcomes.[18]

Secondary changes in the lesions were strongly associated with MCD. Lesions without clear cells (CC) exhibited significantly higher MCD than those with clear cells. This difference may be attributed to the influence of histamine on melanogenesis and the content and structure of melanosomes.[19-22] Additionally, lesions with an angioadnexocentric pattern (AA) demonstrated significantly higher MCD compared to those without this pattern. The angioadnexocentric pattern is primarily observed in benign lesions and may be linked to vascular structure, suggesting that blood vessels in these lesions might lack the same adhesive molecules that facilitate mast cell permeation. Conversely, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), secreted by mast cells, could promote neovascularisation in melanoma, partially explaining the lower MCD values observed, possibly due to the presence of "phantom" mast cells—those that have exhausted their granule enzymes and are not visible on Giemsa stain.[23-25]

Changes in the extracellular matrix (CEM) also significantly influenced MCD variations. Lesions with prominent elastic fibres at the base (CEM-BL), between tumour cells (CEM-TL), or with intratumoral stromal mucin deposition (CEM-S) consistently exhibited higher MCD compared to those without these features. These findings underscore the importance of mast cell recruitment and the alterations in the extracellular matrix.[26-28]

Moreover, all changes mimicking non-melanocytic components (CINC) including lesions with *pseudolacunae*, tubular patterns, C-cell type neurotisation, pseudomeissnerian type neurotisation and lipidation—were associated with significantly higher MCD (Table 2, MW, $p < 0.05$). These architectural features may create microenvironmental conditions conducive to mast cell infiltration, potentially influencing lesion progression or immune modulation, such as mast cell involvement in melanocyte proliferation and neurotisation, or through mast cell-induced changes in melanocyte activity and lipid metabolism.[29-31]

Presented study also confirmed that interactions with adjacent structures, such as the epidermis, were associated with variations in MCD. Lesions exhibiting seborrheic keratosis-like changes (IAS-E) had significantly higher MCD compared to those without this feature. Mast cells may enhance keratinocyte activation through growth factors like mast cell growth factor and stem cell factor. Yamanaka-Takaichi et al[32] demonstrated increased mast cell presence in seborrheic keratosis, supporting their involvement in similar changes in melanocytic lesions. While melanocytic lesions with folliculitis and trichilemmal or epidermal cysts showed increased mast cell presence, this finding was not statistically significant.

In summary, most factors examined in this study were significantly correlated with variations in MCD. According to the Spearman coefficient of determination (ρ^2), types of melanocytic lesions ($\rho^2 = 0.27$) and C-cell type neurotisation (CINC-CN) ($\rho^2 = 0.27$) emerged as the factors most significantly influencing MCD variations, implicating their roles in tumour-protective mechanisms and the maturation of melanocytic nevi.

Conclusion

This study confirmed the variability in MCD within melanocytic lesions, which were significantly correlated with demographic factors, lesion type and histopathological features. Nevi showed higher MCD than melanomas, suggesting mast cells may play a protective role in benign lesions but support tumour growth in malignancies. Epidermo-dermal and intradermal nevi had higher MCD than dysplastic nevi, indicating that reduced MCD influence may contribute to genetic or epigen-

etic abnormalities in dysplastic nevi. Lower MCD in dysplastic nevi may support malignancy in uncertain cases, when combined with other diagnostic criteria. Larger studies where different techniques are compared are necessary to define an MCD threshold for diagnosis. High MCD was linked to extracellular matrix changes—like increased elastic fibres and mucin—which suggest maturation or regression in benign melanocytic lesions. This raises the possibility that mast cells may influence stromal remodelling and contribute to melanoma regression. These findings underscore the complexity of mast cell functions in melanocytic lesions, providing valuable insights into their potential as biomarkers and therapeutic targets.

Ethics

This study not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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