Mast cells in meningiomas

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ABSTRACT

Meningioma represents the most frequent tumor of the central nervous system (CNS). Correlations between the presence of mast cells (MCs) and grade or other histological features of meningioma are still debated. Our study aimed to better understand the relationship between mast cells and meningiomas and to compare our results based on specific histological subtypes and novel 2021 CNS WHO grading system. We observed some differences as regards the number of MCs and meningioma grade. In low-grade (grade 1) meningiomas, MCs were observed in 7/22 cases, while they were consistently present in all eight high-grade cases (grade 2 and grade 3). Among the grade 1 meningiomas, we observed two "low-positive", two "intermediate-positive", and three "high-positive" cases. Among the group of high-grade meningiomas, the six cases grade 2 were considered as "low-positive", while the two grade 3 cases showed a higher number of MCs and were included in the "intermediate-positive" group. Even though with no statistical significance, due to the low number of cases, our results seem to confirm a sort of relationship between meningioma grading and the number of MCs, as demonstrated by the higher percentage of high-grade meningiomas showing MCs infiltrates, compared to low-grade meningiomas.

Key words: angiogenesis; mast cells; meningioma; tumor progression.

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Contributions: DR, AD, study design, manuscript original drafting; AD, RT, TA, AR, data collection and analysis. All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare that they have no competing interests, and all authors confirm accuracy.

Ethical approval: this study was approved by the Institutional Review Board at the Bari Policlinico Hospital, University of Bari "Aldo Moro" (approval protocol n. 6898).

Availability of data materials: the data sets used and analyzed in this study are available from the corresponding author.

Funding: this study was supported by European Union Seventh Framework Program (FPT7/2007-2013) under grant agreement n° 278570 to DR.

Introduction

Meningioma represents the most frequent tumor of the central nervous system (CNS). It commonly arises from the meninges,[1] but in rare cases may also arise outside the CNS, such as in lungs or head and neck.[2,3] Meningiomas are believed to derive from arachnoid cap cells,[4] hence their origin is still debated if it is to be considered mesenchymal or not.

The 5th edition of the World Health Organization (WHO) Classification of CNS Tumors, published in 2021, introduced numerous changes as regards diagnosis, prognosis and molecular features of CNS neoplasms, including meningiomas.[5,6] In 2021 CNS WHO classification, meningiomas represents a single tumor type, composed of 15 histological subtypes. The grading system has been converted into a within-tumor three-tiered grading, independently from histological subtype. Rhabdoid and papillary meningiomas, frequently showing an aggressive behavior, previously belonged to grade 3; however, as demonstrated in recent studies, their morphology is not sufficient to designate them as grade 3, and they are now graded with the same criteria applied for other meningioma subtypes. However, since chordoid and clear cell meningiomas are consistently associated with a higher risk of recurrence, they are assigned as grade 2 only on the basis of their histological appearance.[6]

Angiomatous meningioma is a histological subtype of meningioma characterized, as its name suggests, by the presence of several blood vessels within the tumor. However, the presence of blood vessels, even numerous, is not an unusual feature in meningiomas. Therefore, with the aim of standardizing the histopathological diagnosis, it has been established that the vascular component of a meningioma should exceed 50% of the total tumor area to be defined as angiomatous meningioma.[7] Angiomatous meningiomas are frequently associated with prominent peritumoral brain edema.[8] Previous studies demonstrated that angiomatous and secretory meningiomas exhibit a high density of mast cells (MCs), which tend to accumulate around blood vessels and may be associated with edema production.[9,10] MCs have been detected and correlated with brain edema also in other CNS tumors, including low-grade and high-grade gliomas, hemangioblastomas and brain metastases.[11] Reszec *et al.* evaluated, in two different studies, the presence of MCs in meningiomas with various grades and morphology, using tryptase immunostaining.[12,13] In the first study,[12] MCs were observed in 31.8% of low-grade meningiomas, mostly aggregated around intratumoral blood vessels; in psammomatous, secretory and meningothelial meningiomas MCs were totally absent, whereas in all fibrous and transitional meningiomas were observable. As regards high-grade meningiomas, in 86% of the cases MCs were detected, and were found to be particularly numerous in a single case of anaplastic meningioma (now grade 3, according to 2021 CNS WHO classification). In the second study,[13] MCs were observed in 40.4% of low-grade cases and in 90% of high-grade cases. In the latter, MCs were present not only around blood vessels but also dispersed within the tumor.

To corroborate the findings reported in previous studies, we therefore analyzed the presence of MCs in a cohort of meningiomas (n=30). The aim of our study was to better understand the relationship between MCs and meningiomas, and to compare our results based on specific histological subtypes and novel 2021 CNS WHO grading system. Additionally, we tried to establish whether the presence of MCs might represent a diagnostic clue for angiomatous meningiomas.

Materials and Methods

Thirty meningioma cases at the Bari Policlinico Hospital, University of Bari "Aldo Moro" (2021-2023) have been studied. All cases were diagnosed and revised by two expert neuropathologists, based on the 5th edition of WHO classification. Evaluation of MCs presence was performed using immunohistochemical methods. Formalin-fixed paraffin-embedded (FFPE) tissue samples were sectioned into 4 µm thickness with a microtome and placed on charged microscope slides. Sections were deparaffinized in a tissue-drying oven for 1 h at 60°C, then washed in xylene twice for 10 min at room temperature. Sections were rehydrated in a graded alcohol scale and rinsed in Tris-buffered saline solution (TBS) added with 0.025 Triton X-100 (TBS-Tr). Antigen retrieval was performed in 0.01 M sodium citrate pH 6.0 buffer for 20 min at 96-98°C. Non-specific binding sites were blocked by Dual Endogenous Enzyme-Blocking target (S2003, Agilent Dako, Glostrup, Denmark) for 10 min. Afterwards, the sections were incubated with monoclonal mouse anti-human mast cell tryptase (clone AA1, 1:100 dilution; Dako) or, alternatively, with Ki-67 (1:200, clone MIB-1; Dako). Rinsed in TBS-Tr, sections were incubated with biotinylated polymer and streptavidin-HRP for 10 min each (TP-060-HLX, Thermo Scientific, Fremont, CA, USA). The immunodetection was performed in distillate water with a DAB substrate kit for peroxidase (SK-4100, Vector Laboratories, Burlingame, CA, USA) for 2 min at room temperature. Subsequently, counterstaining for nuclei was performed using Mayer's hematoxylin and slides were mounted with Ecomount (EM897L, Biocare Medical, Prinsessegracht, The Netherlands). Negative controls were prepared by omitting the primary antibodies and mismatching the secondary antibodies. The slides were examined under a light microscope. To avoid false evaluation, immunohistochemical estimation of tryptase-positive MCs was independently performed by two pathologists. Slides were scanned with a Hamamatsu NanoZoomer S60 automatic digital slide scanner (Hamamatsu Photonics, Hamamatsu, Japan), obtaining images of whole stained sections at a resolution of at least 1 pixel per µm. The number of MCs for each case has been manually counted on digital images, as tryptase-positive MCs per 1 mm^2, examining the whole sections. Necrotic areas, pseudopsammoma bodies, edema and cystic spaces were excluded from the MCs count. Based on the number of MCs per 1 mm^2, each case has been classified as: negative (0/1 mm^2);low-positive (<5/1 mm^2); intermediate-positive (5-9/1 mm^2);high-positive (≥10/1 mm^2). Mitotic index was calculated as total number of mitoses observed in 10 high-power fields (400x magnification, 22 mm eyepiece field of view diameter). Statistical analyses using Pearson's and chi-square tests have been made, for each case, to study the correlations between the number of MCs and clinical (sex, age) or histological features (histological subtype, grade, necrosis, brain infiltration, mitoses and Ki-67-proliferative index). Values of $p<0.05$ were considered statistically significant. This study was approved by the Institutional Review Board at the Bari Policlinico Hospital, "Aldo Moro" University of Bari, (approval protocol n. 6898) and conducted in accordance with the Principles of Ethics for Medical Research Involving Human Subjects set out in the Declaration of Helsinki and its subsequent amendments. The patients gave signed informed consent for diagnostic and research analyses.

Results

Patient characteristics, clinical data and histological features were retrieved from hospital records and pathology reports, and are summarized, together with the results of our analysis, in Table 1. We examined 30 cased diagnosed as meningioma at Bari Policlinico Hospital, through a period from 2021 to 2023. 20 patients were female (66.7%), 10 patients were male (33.3%). The mean age was 58.1 years for both sexes, 50.9 for females and 65.5 for males. Twenty-two tumors (73.3%) were diagnosed as low-grade meningiomas (grade 1), eight tumors (26.7%) were estimated as high-grade meningiomas, subdivided into six (20%) grade 2 and two (6.7%) grade 3. Low-grade meningiomas were diagnosed in 16 female patients and in 6 male patients, with a mean age of 59.3 years. High-grade meningiomas were diagnosed in 4 female patients and in 4 male patients, and the mean age was 54.7 years. The differences as regards age and sex in both groups (low-grade and high-grade) were statistically significant ($p<0.05$). According to 2021 CNS WHO classification, all cases have been subclassified based on the histological subtype. Among grade 1 meningiomas, ten cases (33.3%) were diagnosed as meningothelial meningiomas, four (13.3%) as transitional, three (10%) as angiomatous, one (3.3%) as microcystic, one (3.3%) as secretory, one (3.3%) as fibrous, 1one (3.3%) as psammomatous and one (3.3%) as metaplastic, showing bone and adipose tissue formation. Among grade 2 meningiomas, five (16.7%) were diagnosed as atypical meningiomas, and one (3.3%) as rhabdoid. Among grade 3 meningiomas, one (3.3%) was diagnosed as anaplastic and one (3.3%) as papillary. As regards necrosis, which is more frequently observable in high-grade meningiomas, it was detected only in three cases (10%), one assigned to grade 2 and showing rhabdoid morphology, and two assigned to grade 3 and belonging to papillary and anaplastic subtypes, respectively. Brain infiltration, which represents a criterium for the diagnosis of grade 2, was observed in three cases (10%), all assigned to grade 2 and subdivided into two atypical and one rhabdoid meningiomas. Mitotic index was variable and correlated, for each case, with the assigned grade, according to 2021 WHO criteria (Table 1). The proliferative index, calculated as percentage of Ki-67-positive tumor cells, ranged from 1%

Table 1. Summary of clinical and histological features.

Case	Sex	Age	Histological subtype	Grade	Necrosis	Brain infiltration	Mitotic index	Ki-67 (proliferative index)	Mast cells (n/1 mm^2)
1	F	64	Atypical	2	No	No	6/10 HPF	12%	2 (LP)
2	M	75	Angiomatous	1	No	No	<1/10 HPF	2%	15 (HP)
3	F	53	Transitional	1	No	No	<1/10 HPF	3%	0 (N)
4	F	70	Transitional	1	No	No	1/10 HPF	7%	0 (N)
5	M	75	Atypical	2	No	Yes	4/10 HPF	11%	3 (LP)
6	M	64	Fibrous	1	No	No	<1/10 HPF	10%	0 (N)
7	F	19	Psammomatous	1	No	No	<1/10 HPF	3%	0 (N)
8	F	50	Microcystic	1	No	No	<1/10 HPF	3%	8 (IP)
9	F	75	Transitional	1	No	No	<1/10 HPF	3%	0 (N)
10	F	64	Metaplastic	1	No	No	<1/10 HPF	2%	0 (N)
11	F	80	Meningothelial	1	No	No	<1/10 HPF	2%	0 (N)
12	F	76	Transitional	1	No	No	<1/10 HPF	1%	0 (N)
13	M	74	Atypical	2	No	Yes	5/10 HPF	10%	2 (LP)
14	F	42	Papillary	3	Yes	No	21/10 HPF	10%	7 (LP)
15	F	43	Meningothelial	1	No	No	<1/10 HPF	8%	0 (N)
16	F	44	Rhabdoid	2	Yes	Yes	7/10 HPF	16%	2 (LP)
17	M	67	Meningothelial	1	No	No	3/10 HPF	8%	0 (N)
18	M	74	Meningothelial	1	No	No	3/10 HPF	6%	0 (N)
19	F	70	Secretory	1	No	No	<1/10 HPF	3%	7 (IP)
20	M	47	Atypical	2	No	No	5/10 HPF	20%	3 (LP)
21	M	59	Angiomatous	1	No	No	<1/10 HPF	3%	18 (HP)
22	F	37	Meningothelial	1	No	No	<1/10 HPF	8%	2 (LP)
23	F	50	Meningothelial	1	No	No	<1/10 HPF	1%	0 (N)
24	M	53	Anaplastic	3	Yes	No	22/10 HPF	35%	6 (LP)
25	F	59	Meningothelial	1	No	No	<1/10 HPF	2%	1 (LP)
26	F	45	Angiomatous	1	No	No	<1/10 HPF	1%	12 (HP)
27	M	67	Meningothelial	1	No	No	<1/10 HPF	3%	0 (N)
28	F	39	Atypical	2	No	No	7/10 HPF	14%	2 (LP)
29	F	55	Meningothelial	1	No	No	<1/10 HPF	2%	2 (LP)
30	F	53	Meningothelial	1	No	No	<1/10 HPF	8%	0 (N)

HPF, high power fields; N, negative; LP, low-positive; IP, intermediate-positive; HP, high-positive.

to 35%, with a mean value of 7%. Higher values of both mitotic and proliferative index correlated with high-grade meningiomas, compared to low-grade cases ($p<0.05$).

Tryptase-positive MCs were observed in 16 out of 30 meningioma cases (53.3 %), while in the remaining 14 cases (47.7%) MCs were absent, hence the cases have been considered as "negative". We did not find any statistically significant correlation between the number of MCs and the examined clinical and pathological features (sex, age, histological subtype, necrosis, brain infiltration, mitotic index and proliferative index). However, we report in a descriptive manner our findings, which may possibly suggest relevant considerations. Considering the 16 positive cases, MCs were observed principally next to blood vessels, but they were also scattered within the tumor. As regards low-grade (grade 1) meningiomas, MCs were observed in 7 out of 22 cases (31.8%). In high-grade meningiomas, MCs were observed in all the eight cases (100%), six grade 2 and two cases grade 3. As regards the grade 1 positive cases, two cases were considered "low-positive" (<5 MCs / 1 mm^2), two cases "intermediate-positive" (5-9 MCs / 1 mm^2), and three cases "high-positive" (≥10/1 mm^2) (Figure 1). As regards the histological subtype, the low-positive cases were both meningothelial and showed 2 MCs / 1 mm^2. The intermediate-positive cases were represented by a secretory and a microcystic meningiomas, with 7 MCs / 1 mm^2 and 8 MCs / 1 mm^2, respectively. Interestingly, all the three high-positive cases showed an angiomatous morphology, characterized by numerous blood vessels and stromal edema. In these cases, MCs were principally aggregated around blood vessels and next to intratumoral edematous areas. As regards the high-grade group, they were all five cases were atypical (grade 2), one was rhabdoid (grade 2), one was anaplastic (grade 3) and one papillary (grade 3). Grade 2 cases showed several MCs lower than 5 / 1 mm^2, hence were included in the low-positive group. The two grade 3 cases showed a higher number of MCs (6 / 1 mm^2 for the anaplastic;7 / 1 mm^2 for the papillary) and were included in the intermediate-positive group. The results regarding the number of MCs observed for each grade and histological subtype are summarized in Figure 2.

Discussion

Meningiomas are common primary neoplasms of the CNS, but correlations between presence of MCs and grade or other histological features of meningioma are still debated. MCs comprise a different myeloid-derived cell category in meningiomas.[12-14] A high number of MCs in tumors has been generally associated with poor outcomes, due to the numerous tumor-promoting roles that MCs may exert. In fact, MCs may activate several angiogenetic pathways to induce tumoral angiogenesis.[15] Moreover, MCs may regulate the expression of the H1 histamine receptor, which plays a role in tumor cell proliferation and vascular permeability.[16] The relationship between number of MCs and meningioma behavior is uncertain. Some studies reported that presence of MCs was more pronounced in high-grade meningiomas,[12-14] while other studies found no relation between meningioma grade and MCs.[17] Particularly, an increased number of tryptase-positive MCs has been specifically observed in WHO grade II and grade III meningiomas, which is consistent with a potential propensity for meningioma recurrence and aggressive behavior.[12,13] In our study we observed some differences as regards number of MCs and meningioma grade. In low-grade (grade 1) meningiomas, MCs were observed in 7/22 cases, while they were consistently present in all the 8 high-grade cases (grade 2 and grade 3). Among the grade 1 meningiomas, we observed two "low-positive", two "intermediate-positive", and three "high-positive cases. Among the group of high-grade meningiomas, the six cases grade 2 were considered as "low-positive", while the two grade 3 cases showed a higher number of MCs and were included in the "intermediate-positive" group. Even though with no statistical significance, probably due to the low number of cases, our results seem to confirm a sort of relationship between meningioma grading and number of MCs, as demonstrated by the higher percentage of high-grade meningiomas showing MCs infiltrates, compared to low-grade meningiomas. Moreover, this relationship is also highlighted by the increased number of MCs in high-grade meningiomas when comparing grade 2 and grade 3 cases, suggesting a parallel increment of MCs together with the rise of the tumor grade and, contextually, with a poorer prognosis and a more aggressive behavior. However, this relationship between MCs and grading seems to be not valid for some histological subtypes of grade 1 meningiomas. Previous studies reported that secretory and angiomatous meningiomas show a higher density of MCs, compared to other histological subtypes.[9,10] Tirakotai *et al.* examined fourteen cases of secretory

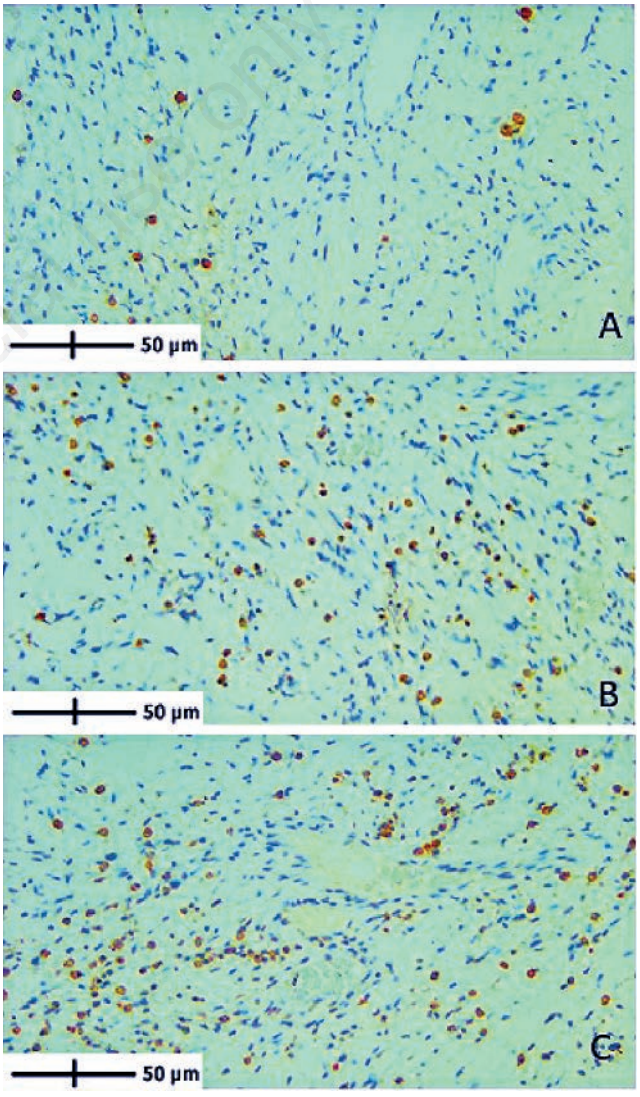

Figure 1. Examples of "low-positive" (<5 MCs / 1 mm^2) (**A**), "intermediate-positive" (5-9 MCs / 1 mm^2) (**B**) and "high-positive" (≥10/1 mm^2) (**C**); meningioma samples stained with a monoclonal mouse anti-human MCs tryptase (clone AA1, DAKO;1:100 dilution). Original magnification: 20 x.

meningiomas, and found a significantly increased number of MCs compared to an equal number of non-secretory meningiomas of different grades.[10] Reszec *et al*. evaluated, in two different studies, the presence of MCs in meningiomas, using tryptase immunostaining and comparing different grades and histological subtypes.[12,13] In a study published in 2012,[12] MCs were observed in 31.8 % of grade 1 meningiomas, particularly in fibrous and transitional histological subtypes. On the other hand, MCs were detected in 86% of the high-grade cases, being more numerous in a single case of anaplastic meningioma. In the second study, published in 2013,[13] MCs were observed in 40.4% of low-grade and in 90% of high-grade meningiomas, but the differences between histological subtypes were not furtherly investigated. Bujan *et al*. observed a significantly higher percentage of MCs in angiomatous meningiomas compared to other histological subtypes.[9] Similar findings have been also reported in a previous study from the same group.[10] In our study, we observed a different number of MCs in different histological subtypes. As regards grade 1 cases, we observed two low-positive meningothelial meningiomas, one intermediate-positive secretory meningioma, one intermediate-positive microcystic meningioma and, interestingly, three high-positive cases all belonging to the angiomatous subtype. In all these cases, MCs were mainly aggregated around blood vessels and close to areas with stromal edema, similarly to what observed in other studies.[12,13] Our results are consistent with findings reported in previous studies and furtherly suggest a possible correlation between MCs and angiomatous meningioma. MCs frequently tend to accumulate around blood vessels and seem to be related with an increased risk of peritumoral brain edema.[10] MCs have been correlated with development of brain edema also in other tumors of the CNS, including gliomas and brain metastases.[11] MCs may release proteolytic enzymes capable of degrading components of the blood-brain barrier basal lamina, such as collagen IV, and tight junction proteins, provoking vascular leakage which leads to edema formation.[18] Moreover, MCs may secrete different mediators which are likely to contribute to brain edema, such as histamine, serotonin, and vascular endothelial growth factor;[11] also hypoxia and hypoxia inducible factor-1 (HIF-1) have been reported to play an important role.[13] In our study we did not evaluate the correlation between MCs and brain edema formation, but this may represent a possible aim for future studies, together with the evaluation and comparing of various mediators expression in different meningioma grades and histological subtypes. However, based on our results and in accordance with the findings reported in previous studies, a high number of MCs, along with an elevated number of intratumoral blood vessels may be considered as an additional diagnostic criterion for the histological diagnosis of angiomatous meningioma. In this study, the density of vessels was not quantitatively assessed and may represent a possible limitation; however, it could be a valuable parameter to be investigated in future studies. Moreover, further studies with a larger number of cases are surely needed to confirm the possible correlation between MCs and angiomatous histological subtypes. Furthermore, clinicopathological studies on wide number of cases and including long follow-up periods, will be vital to eventually demonstrate whether the number of MCs is also correlated with higher grades and, consequently, with poorer outcomes for meningiomas.

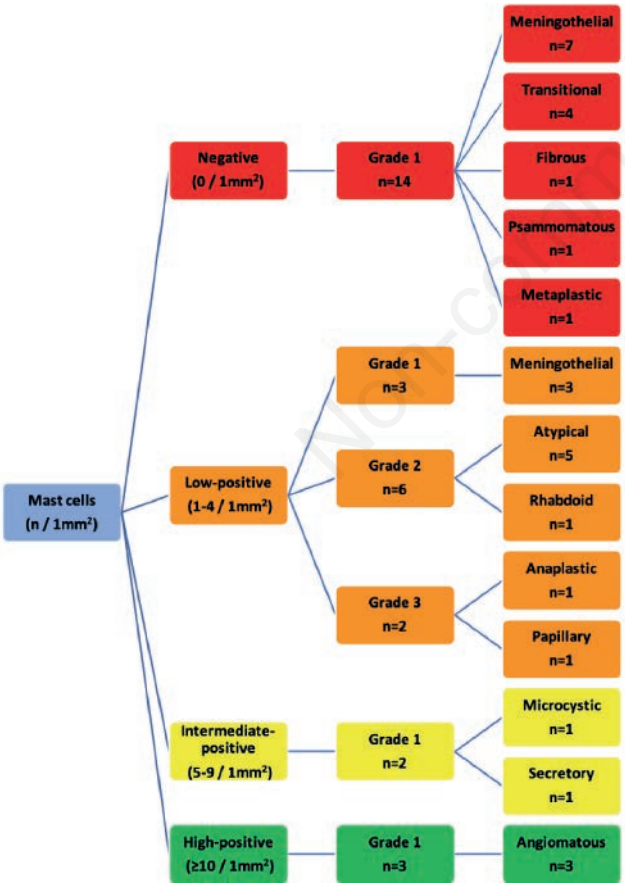

Figure 2. Graphical plot, representing the results as regards the number of mast cells observed for each grade and histological subtype.

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Received: 19 January 2024. Accepted: 19 March 2024.

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European Journal of Histochemistry 2024; 68:3973
doi:10.4081/ejh.2024.3973