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ORIGINAL ARTICLE

Mast cells in central nervous system neoplasms: an immunohistochemical study

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Abstract

Objective: *To investigate the relationship between mast cells (MCs) and different central nervous system (CNS) tumors.* **Methods***: It was a comparative immunohistochemical study to investigate the presence, number, and location of MCs in pilocytic astrocytomas, glioblastoma, medulloblastoma, ependymoma, meningioma, and immature and mature teratomas. Means, medians, and standard deviation were obtained. Comparation in the number of MCs in the different tumors was carried out using the Mann–Whitney test ($p < 0.05$).* **Results:** *There was a significant difference in the number of MCs between pilocytic astrocytoma ($\bar{X} = 0$), and mature teratoma ($\bar{X} = 65$), in relation to the other neoplasms ($\bar{X} = 3\text{-}11.4$). MCs were identified in meningeal lining in meningiomas, in the perivascular space in ependymomas and in the tumor stroma and perivascular space in the rest of the tumors analyzed.* **Conclusions:** *MCs appear to play different roles in CNS tumors. Its absence in pilocytic astrocytomas and its presence in glioblastomas suggests a role in the latter, probably related to angiogenesis. The maximum number of MCs was observed in mature teratomas, specifically in relation to stratified squamous epithelium, possibly in relation to trophic factors that contribute to epithelial renewal and maintenance. These findings call for future research to determine if MCs can be a therapeutic target or are important as a prognostic factor.*

Keywords: *Mast cells. Brain tumors. Glioblastoma. Teratoma. Meningioma.*

Las células cebadas en neoplasias del sistema nervioso central: un estudio inmunohistoquímico

Resumen

Objetivo: *Investigar la relación entre las células cebadas (CCs) y diferentes tumores del sistema nervioso central (SNC).* **Métodos:** *Fue un estudio inmunohistoquímico comparativo para investigar la presencia, el número y la ubicación de CCs en astrocitomas pilocíticos, glioblastoma, meduloblastoma, ependimoma, meningioma y teratomas inmaduros y maduros. Se obtuvieron medias, medianas y desviación estándar. La comparación en el número de CCs en los diferentes tumores se realizó mediante la prueba de Mann Whitney ($p < 0,05$).* **Resultados:** *Hubo diferencia significativa en el número de CCs*

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entre el astrocitoma pilocítico ($\bar{X}$ = 0) y el teratoma maduro ($\bar{X}$ = 65), con relación a las demás neoplasias ($\bar{X}$ = 3-11,4). Se identificaron CCs en el revestimiento meníngeo en los meningiomas, en el espacio perivascular en los ependimomas y en el estroma tumoral y el espacio perivascular en el resto de los tumores analizados. **Conclusiones:** *Las CCs parecen desempeñar diferentes funciones en los tumores del SNC. Su ausencia en los astrocitomas pilocíticos y su presencia en los glioblastomas sugiere un papel en estos últimos, probablemente relacionado con la angiogénesis. El máximo número de CCs se observó en teratomas maduros, específicamente en relación con el epitelio escamoso estratificado, posiblemente en relación con factores tróficos que contribuyen a la renovación y mantenimiento del epitelio. Estos hallazgos requieren investigaciones futuras para determinar si los MC pueden ser un objetivo terapéutico o si son importantes como factor pronóstico.*

Palabras clave: *Mastocitos. Tumores cerebrales. Glioblastoma. Teratoma. Meningioma.*

Introduction

Mast cells (MCs) are versatile; they can have a neoplastic behavior or, more frequently, become activated and have an active participation in different pathologies. Clonal proliferations are frequently associated with genetic mutations such as gain-of-function D816V. In this context, we can find cutaneous and systemic mastocytosis and clonal/monoclonal mast cell activation disorders or syndromes. MCs can undergo activation secondary to allergic, paraneoplastic, and inflammatory diseases[1].

One field of research is the participation of MCs in central nervous system (CNS) neoplasms. The clinical manifestations and the brain tumor progression in a patient depend on the interaction between neoplastic cells and brain tissue, in a specific microenvironment[2]. In this microenvironment, the immune system plays an important role, as well as mechanical, biochemical and molecular factors[3]. MCs seem to modulate the behavior of tumor cells and tumor microenvironment (TME). Tumor-associated MCs have been found to be a favorable prognostic factor in some malignant neoplasms such as diffuse large B-cell lymphoma, esophageal adenocarcinoma, and ovarian cancer, but have poor or mixed prognosis in lung, gastric and breast cancers, and in melanoma[4].

The participation of MCs is complex. On one hand, they release proinflammatory mediators contained in their granules in response to pathological events, which allows other immune system cells to be activated and many of them cross the blood–brain barrier (BBB) to exert their action. However, MCs also produce growth and angiogenic factors that may play an important role in the genesis and the growth of tumors[5].

Therefore, the present work seeks to know the relationship that MCs have with different CNS tumors through a comparative immunohistochemical study on the presence, number, and location of these cells. This information is important to understand the behavior of MCs in different brain neoplasms and identify possible therapeutic strategies.

Methods

Type of study

It was a retrospective and comparative study, where biopsies of human brain tumors were analyzed.

Ethical considerations

The protocol was approved by the Ethics and Research Committees of the Faculty of Medicine, Veracruz, of the Universidad Veracruzana (2021-47). It was a retrospective study, in which personal data of the participants were not handled; informed consent was not considered necessary for this study. Patient consent was not required in accordance with local and national guidelines. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Sample

Twenty-nine recent cases (n = 29) of brain tumors were selected at convenience from the pathology department of a referral hospital in Mexico. Of the total population, 18 were men and 11 women, with an age range of ~ 1-65 years. Clinical records were reviewed. The types of tumors analyzed are shown in table 1 and included grades I-IV neoplasms (the WHO classification)[6].

Technique

The slides of the selected cases were reviewed and the histological diagnosis was corroborated. Paraffin

Table 1. Patient demographics and location of the tumor

ID	Sex	Age (years)	Histopathological diagnosis/Grade (WHO)	Location
1	F	18	Pilocytic astrocytoma (I)	Hypothalamic region
2	M	12	Pilocytic astrocytoma (I)	Cerebellar hemisphere
3	F	5	Pilocytic astrocytoma (I)	Cerebellar hemisphere
4	F	15	Pilocytic astrocytoma (I)	Cerebelar vermis
5	M	9	Pilocytic astrocytoma (I)	Cerebellar hemisphere
6	F	33	Ependymoma (II)	Fourth ventricle
7	M	13	Ependymoma (II)	Fourth ventricle
8	M	35	Ependymoma (II)	Fourth ventricle
9	F	10	Ependymoma (II)	Fourth ventricle
10	M	50	Glioblastoma (IV)	Right temporal, parietal, and occipital lobes
11	M	37	Glioblastoma (IV)	Left frontal and parietal lobes
12	F	5	Glioblastoma (IV)	Left frontal and parietal lobes
13	F	29	Glioblastoma (IV)	Right frontal lobe
14	F	68	Glioblastoma (IV)	Right insula
15	F	2	Medulloblastoma (IV)	Cerebelar vermis
16	M	3	Medulloblastoma (IV)	Cerebelar vermis
17	M	30	Medulloblastoma (IV)	Right cerbellar hemisphere
18	M	0.75	Medulloblastoma (IV)	Cerebelar vermis
19	M	26	Medulloblastoma (IV)	Right cerbellar hemisphere
20	F	62	Meningioma (I)	Right tentorium
21	M	28	Meningioma (I)	Right frontal lobe
22	M	28	Meningioma (I)	Right frontal lobe
23	M	52	Meningioma (I)	Sphenoid wing
24	F	48	Meningioma (I)	Cerebellar pontine angle
25	M	5	Inmature teratoma (II)	Pineal region
26	M	5	Inmature teratoma (II)	Pineal region
27	M	6	Mature teratoma	Suprasellar region
28	M	7	Mature teratoma	Pineal region
29	M	7	Mature teratoma	Pineal región

M: male, F: female.

blocks were obtained. They were sectioned and the slides were stained for hematoxylin and eosin, and immunohistochemistry for tryptase (Anti-Mast Cell Tryptase Monoclonal Antibody, unconjugated, clone 10D11, Leica Biosystems®) in an automated process using Leica Bond-III® equipment.

The slides were examined under a light microscope. The number of MCs was counted in triplicate, at 400-fold magnification; the location of these cells (in tumor cells, in the tumor stroma, perivascular, in leptomeninges, in specific tissue structures or components) was also analyzed.

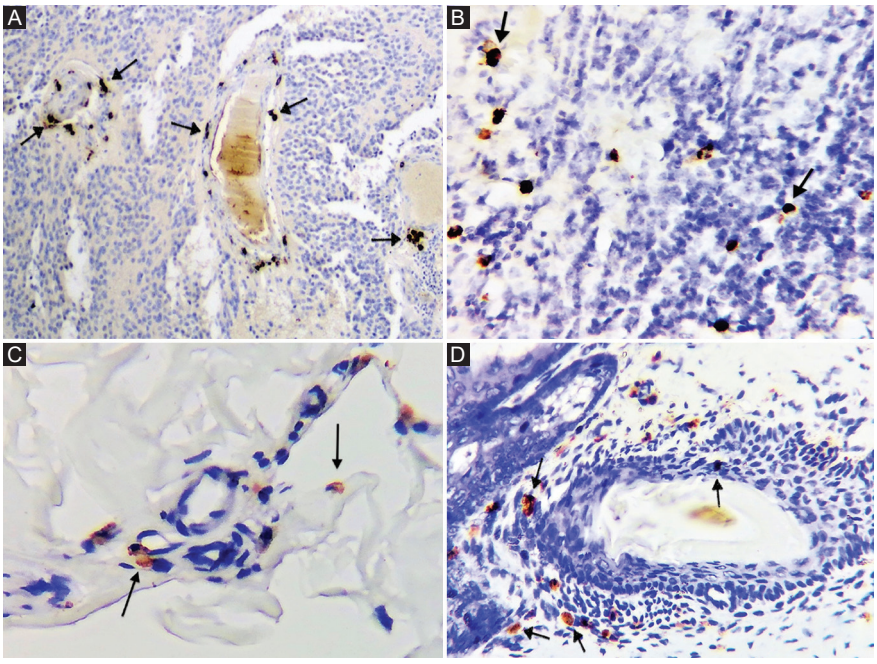

Figure 1. Mast cells (arrows) in different CNS tumors. *Ependymoma*. MC in a perivascular location (A) *Medulloblastoma*. MCs were observed both, in the perivascular space and in the tumor stroma (arrow) (B). *Meningioma*. MC was observed predominantly in the meningeal lining that covered the tumor (C). *Mature teratoma*. MC was associated predominantly, with the squamous epithelium (D). Immunohistochemistry, tryptase antibody, 100 and 400X.

Statistical analysis

Descriptive statistics with means and standard deviation were used. To compare the number of MCs between the different groups of neoplasms (Pilocytic astrocytoma, ependymoma, glioblastoma, medulloblastoma, meningioma, mature teratoma, and immature teratoma), the non-parametric Mann–Whitney test was used and $p < 0.05$ was considered significant. Statistical analysis was performed with IBM® SPSS® Statistics V. 26 software.

Results

The demographic data of the patients and the characteristics of the neoplasms, including type, histological grade, and location are shown in table 1.

Pilocytic astrocytomas

The average age of the patients was 11.8 years. With the exception of the hypothalamic region, all were located in the cerebellum. None of the tumors showed MCs infiltrate.

Ependymoma

The average age of the patients was 22.7 years. All were infratentorial, in relation to the IV ventricle. On average, there were 8.1 MC/10 high power fields (HPF), in a perivascular location, as shown in figure 1A.

Glioblastoma (adult-type diffuse glioma-wild type)

The average age of the patients was 37.8 years. All tumors were supratentorial. There were, on average, 3.4 MCs/10 HPF, and they were observed in both, perivascular space and the tumor stroma.

Medulloblastoma NOS

The average age of the patients was 12.3 years. There were three tumors in the vermis, and two in the cerebellar hemispheres. In these tumors, 5.2 MCs/HPF were quantified. MCs were observed both, in the perivascular space and in the tumor stroma (Fig. 1B).

Table 2. Comparative analysis of the number of MCs between different tumors of the central nervous system

Tumor	Means	SD	Tumor	Means	SD	Mann–Whitney	p
Pylocitic astrocytoma	0.00	0.00	Ependymoma	8.13	5.98	0.00	0.007
			Glioblastoma	3.40	2.88	0.00	0.005
			Medulloblastoma	5.20	4.66	2.50	0.019
			Meningioma	11.40	17.29	0.00	0.005
			Mature teratoma	65.00	42.51	0.00	0.010
			Inmature teratoma	3.00	1.41	0.00	0.016
Ependymoma	8.13	5.98	Glioblastoma	3.40	2.88	3.5	0.108
			Medulloblastoma	5.20	4.66	6.5	0.389
			Meningioma	11.40	17.29	9.5	0.902
			Mature teratoma	65.00	42.51	0	0.034
			Inmature teratoma	3.00	1.41	2	0.355
Glioblastoma	3.40	2.88	Medulloblastoma	5.20	4.66	10.50	0.671
			Meningioma	11.40	17.29	7.00	0.243
			Mature teratoma	65.00	42.51	0.00	0.024
			Inmature teratoma	3.00	1.41	4.50	0.844
Medullo-blastoma	5.20	4.66	Meningioma	11.40	17.29	10.5	0.674
			Mature teratoma	65.00	42.51	0	0.025
			Inmature teratoma	3.00	1.41	4	0.699
Meningioma	11.40	17.29	Mature teratoma	65.00	42.51	1.00	0.050
			Inmature teratoma	3.00	1.41	4.00	0.688
Mature teratoma	65.00	42.51	Inmature teratoma	3.00	1.41	0.00	0.083

SD: Standard deviation

Meningioma

The average age of the patients was 43.6 years. There were two right frontal tumors, one was dependent on the tentorium, one on the sphenoid wing, and the other on the cerebellar-pontine angle. Meningiomas showed 11.40 MCs/HPF, and they were observed predominantly in the meningeal lining that covered the tumor (Fig. 1C).

Immature teratoma

The average age of the patients was 5 years. Both were pineal region tumors, and three MCs/HPF were quantified. MCs were observed predominantly in the tumoral stroma.

Mature teratoma

The average age of the patients was 6.6 years. Two were pineal region tumors, and one had suprasellar location. In these neoplasms, 65 MCs/HPF were quantified, and asso-ciated predominantly, with the squa-mous epithelium while were very scarce in other tissues of the tumor (Fig. 1D).

Statistical analysis

Results are shown in table 2.

Discussion

Most of the information available regarding MCs in neoplasms of the CNS is related to meningiomas. They

have been observed in a perivascular arrangement in 90% of high-grade meningiomas and have been associated with brain edema[7]. MCs have cytoplasmic granules and secrete chemokines and cytokines that can disrupt the BBB; also, these cells have angiogenic mediators that may contribute to tumor development[7]. Knowing the cells of the immune system, which participate in the TME of neoplasms, are the beginning for molecular studies that allow to understand the interaction mechanisms and to contribute to the discovery of prognostic factors and new therapeutic targets[7]. In fact, a tumor stroma rich in B lymphocytes and MCs has recently been described in the G4 molecular subgroup of medulloblastomas, which may be a marker of better prognosis[8].

Although there are studies of individual tumors (meningiomas, medulloblastomas, etc.), there are no comparative studies between different types of neoplasms in the CNS; this information is useful because it allows to show other types of relationships between MCs and neoplastic cells. For example, the maximum number of MCs/10 HPF was observed in relation to the mature squamous epithelial component of the teratomas. Mature teratoma seems to be a study model for MCs tissue affinity. It was evident the tropism of these cells for the stratified squamous epithelium, despite the fact that other mature tissues were available. MCs produce many trophic factors, but it is well known that histamine induces epithelial cell proliferation[9]. MCs also produce heparin that increases epithelial proliferation in a dose-dependent manner and inhibits the growth of associated mesenchyme[10]. Furthermore, epidermal secretion of CCL2 and CCL5 chemokines attracts MCs[10].

In meningiomas, MCs were located predominantly in the leptomeninges. The perivascular zones were the seat of MCs in ependymomas, medulloblastomas, and glioblastomas; these past two cases also showed the presence of MCs in the intratumoral stroma. However, the circumscribed glioma, pilocytic astrocytomas, did not show MCs.

Location of MCs in the analyzed tumors was not related to a histologically evident inflammatory process. Therefore, why is there a different number and distribution of MCs in different CNS tumors? MCs are able to migrate from blood to brain parenchyma and in pathological conditions may disrupt BBB and induce basal lamina degradation, releasing TNF-α, and matrix metalloproteinases MMP-2 and MMP-9[11]. *In vitro* has been demonstrated that MCs infiltrate gliomas in response to different tumor signals, including IL-6, initiating a dialogue between neoplastic and MCs[12]. TME is important in the interaction and includes tumor and non- tumor resident cells. In the case of glioblastoma and medulloblastoma, both, grade IV tumors, MCs were observed not only perivascularly, but also in the tumor stroma. Tumor-associated MCs that infiltrate solid tumors are controversial, because depending of the tumor, may have pro-tumoral (promoting angiogenesis, fibrosis, metastasis, and lymph angiogenesis) or anti-tumoral behavior[13]. Glioblastoma cells can recruit other cells of the host organism to promote their growth. Glioblastoma induces immune-depressive effects, especially through two transcription factors, SRY-box transcription factor 2 (Sox2), and octamer-binding transcription factor 4 (Oct 4), that when activated promote suppression of innate and adaptative immune responses, and maintain glioma cell stemness and tumor-propagating activity[14]. In the case of MCs, it is possible that their presence contributes to the disruption of the BBB and the accompanying edema observed in glioblastoma, but it is also possible that the tumor manipulates these cells to promote angiogenesis through production by MCs of vascular endothelial growth factor (VEGF). Production of IL-6 by the tumor cells induces VEGF production by MCs, *in vitro* and, at the same time, induces survival of MCs[14]. However, in spite that, pilocytic astrocytomas are vascularized neoplasms, do not show MCs. This neoplasm is grade I-tumor with a low growth rate; more research is needed in this field[14].

In the case of medulloblastoma (MB), in patients with Group 4 tumors, tumor-infiltrating B-cells (TIL-Bs) enrichment has been described. Patients with a high-level of TIL-Bs had better 5-years survival. Interestingly, MCs in Group 4 MB correlated positively with TIL-Bs[8]. Group 4 medulloblastomas account for 35% of MBs and are characterized by amplification of the MYCN proto-oncogene, isochromosome 17q, and frequently, duplication of gene SNCAIP (synuclein alpha interacting protein)[15]. In an angiogenesis study in MB, distribution of toll-like receptor 2 (TLR2), and receptor for advanced glycosylation end-product (RAGE), as well as the location of MCs were studied. MCs were observed in the perivascular space of large brain and meningeal vessels at the border of tumor, associated with RAGE+ receptors, while TLR2 was positive in angiogenesis at necrotic areas[16]. A targeted study is required to investigate the involvement of MCs in the different MB subgroups.

Paul Ehrlich described MCs, in 1878; they have a wide distribution and are strategically located at the interface between the organism and the environment (skin, gastrointestinal tract, and respiratory mucosa) and participate in type I hypersensitivity reactions. The immature progenitor cells (CD34+ and CD117+) migrate

from bone marrow to peripheral tissues where they finally mature[17]. At the CNS, MCs are normally found in the brain side of the BBB and in the leptomeninges[18]. Under physiological conditions, their number is scarce; however, they maintain constant communication with neurons, astrocytes, microglia, and endothelial cells.

In the communication between neurons and MCs, the formation of synaptic-like structures favored by adhesion molecules such as N-cadherin or synaptic cell adhesion molecule (SynCAM) has been described[19]. Serotonin produced by MCs contributes to neurogenesis and to the behavioral and physiological function of the hippocampus. Serotonin is a trophic factor synthesized by both, MCs, and neurons[20]. MCs also interact with astrocytes and microglia. It has been shown that microglia constitutively expresses the four histamine receptors (H1R, H2R, H3R, and H4R) and there is a selective upregulation of receptors H1R and H4R in response to histamine[21].

On the other hand, astrocytes bear histamine receptors H1R and H2R and coincide with MCs in the perivascular space, in the thalamus, hypothalamus and in the pineal region[22]. Recognition between these two cells takes place through the interaction of CD40-CD40 ligand[23]. The immune microenvironment of meningiomas includes macrophages, T-cells, and MCs. Expression of tryptase was observed in 32% of low-grade meningiomas and 86% of high-grade meningiomas, close to blood vessels[24]. Both, meningiomas and MCs can secrete VEGF; intracranial meningiomas have been associated with brain edema in 50-66% of cases. It seems to be an association of MCs with perivascular edema and with disruption of the BBB, especially in secretory meningiomas characterized by infiltration by many of MCs[25]. In our study, all cases of meningioma (the WHO I) showed MCs, predominantly in the meningeal lining that covered the tumor and also, in perivascular distribution.

We must consider that the groups of tumors analyzed were small; however, the difference in the number of cells observed in pilocytic astrocytomas and mature teratomas was evident. If larger groups are compared, statistically significant differences can probably be observed even between some subtypes of the same tumor type.

Conclusions

This work demonstrated that MCs involvement varies in different tumors; from neoplasms with absent MCs, such as pilocytic astrocytomas, to tumors with abundant MCs with special trophism toward the stratified squamous epithelium component in mature teratomas. In this spectrum, MCs were found in smaller numbers in the other tumors studied, with spatial distribution in perivascular ependymomas and in the leptomeningeal lining in meningiomas. It is necessary to study the mechanisms of interaction of these cells in the different TMEs, especially to identify possible therapeutic targets and prognostic factors.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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