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Immunohistochemical expression of Cyclin D1 and c-MYC proteins in intracranial meningioma

Expressão imunoistoquímica das proteínas Ciclina D1 e c-MYC em meningiomas intracranianos

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ABSTRACT

Introduction: Intracranial meningioma is the most frequent tumor of the central nervous system and immunohistochemical markers are important to aid in targeted therapy and prognosis.

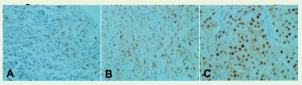
Objective: To evaluate the expression of cyclin D1 and c-MYC markers in intracranial meningiomas and to correlate it with the aggressiveness and recurrence of these tumors.

Method: Retrospective, observational, cross-sectional study using data from the medical records of patients diagnosed with intracranial meningioma who were hospitalized and underwent surgical resection. Epidemiological, clinical and radiological data were collected and recorded. Immunohistochemistry for cyclin D1 and c- MYC markers was performed on all samples. The data regarding the histological grade of the tumors were crossed with the result obtained by immunostaining.

Result: 51 patients were included (72.5% women and 27.5% men) with a mean age of 53.5 years. Headache was the most common symptom and tumors located at the base of the skull accounted for 53% of cases. Grade I meningiomas were detected in 58.8%, grade II in 29.4% and grade III in 9.8%. Tumor recurrence was observed in two cases (3.9%) and disease-free patients corresponded to 49%. The mean follow-up time was 798 days (13-2267). Cyclin D1 was identified in 100% of meningiomas and the intensity of its expression was weak in 52.4% of grade I lesions, moderate in 50% of grade II tumors and strong in 100% of grade III tumors ($p<0.001$). c-MYC was identified in 17.7% (4.7% grade I, 66.7% grade II and 100% grade III) and its expression was weak in 50% in grade II and moderate in 100% in grade III ($p<0.001$). The presence of markers had no statistically significant relationship with patient outcomes.

Conclusion: Cyclin D1 was expressed in all samples of meningiomas and the c-MYC was expressed in 18% of cases. The higher the histological grade, the more intense was the expression of the markers. There was no evidence of a relationship between the markers and tumor recurrence.

KEYWORDS: Meningioma. Cyclin D1. Proto-oncogene proteins. c-MYC.



Cyclin D1: A) weak; B) moderate; c) Strong

Central message

Intracranial meningioma is the most frequent tumor of the central nervous system and immunohistochemical markers are important to aid in targeted therapy and prognosis. This study evaluates the expression of cyclin D1 and c-MYC markers in intracranial meningiomas, correlating them with tumor aggressiveness and recurrence.

Perspective

Cyclin D1 was expressed in all meningioma samples and the marker c-MYC in 18% of the cases, and the higher the histological grade, the more intense the expression of the markers. There was no evidence of a relationship between the markers and tumor recurrence.

RESUMO

Introdução: Meningioma intracraniano é o tumor mais frequente do sistema nervoso central e marcadores imunoistoquímicos são importantes para auxiliar na terapia alvo e prognóstico.

Objetivo: Avaliar a expressão dos marcadores ciclina D1 e c-MYC em meningiomas intracranianos e correlacioná-la com a agressividade e recorrência desses tumores.

Método: Estudo retrospectivo, observacional, transversal utilizando dados dos prontuários de pacientes com diagnóstico de meningioma intracraniano que foram internados e submetidos à ressecção cirúrgica. Os dados epidemiológicos, clínicos e radiológicos foram coletados e anotados. Foi realizada imunoistoquímica para os marcadores ciclina D1 e c-MYC em todas as amostras. Os dados referentes ao grau histológico dos tumores foram cruzados com o resultado obtido pela imunomarcação.

Resultado: Foram incluídos 51 pacientes (72,5% mulheres e 27,5% homens) com média de 53,5 anos. Cefaleia foi o sintoma mais comum e tumores localizados na base do crânio representaram 53% dos casos. Meningiomas grau I foram detectados em 58,8%, grau II em 29,4% e grau III em 9,8%. Recidiva tumoral foi observada em 2 casos (3,9%) e pacientes livres de doença corresponderam a 49%. A média do tempo de seguimento foi de 798 dias (13-2267). A ciclina D1 foi identificada em 100% dos meningiomas e a intensidade de sua expressão foi fraca em 52,4% das lesões grau I, moderada em 50% dos tumores grau II e forte em 100% dos tumores grau III ($p<0,001$). c-MYC foi identificado em 17,7% (4,7% grau I, 66,7% grau II e 100% grau III) e sua expressão foi fraca em 50% no grau II e moderada em 100% do grau III ($p<0,001$). A presença dos marcadores não teve relação estatisticamente significativa com o desfecho dos pacientes.

Conclusão: A ciclina D1 apresentou expressão em todas as amostras de meningiomas e o marcador c-MYC em 18% dos casos. Quanto maior o grau histológico mais intensa foi a expressão dos marcadores. Não se evidenciou relação dos marcadores com a recorrência tumoral.

DESCRITORES: Meningioma. Ciclina D1. Proteínas proto-oncogênicas. c-MYC.

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INTRODUCTION

Meningioma is the most common intracranial tumor, corresponding to 38.3% of primary neoplasms of the central nervous system (CNS) and 54.5% of its benign lesions. Although considered the most common primary brain tumor (8.81/100,000 population), it represents only 1.5% of malignant CNS lesions.[1] Characteristically, the incidence increases with age, especially after 45 years of age, affecting women more frequently.[1]

The World Health Organization classifies meningiomas into 3 histological grades: benign (grade I), atypical (grade II) and anaplastic (grade III). Grade I and II meningiomas are the most common, accounting for 80.3% and 17.9%, respectively, and 1.6% consist of grade III.[1] Since this tumor grows slowly, early detection can be challenging due to the absence of relevant clinical symptoms at the beginning of the disease. The most common symptoms are headache, focal neurological deficits, seizures, personality changes, mental confusion, and altered level of consciousness. Many lesions are diagnosed incidentally, known as incidentalomas. The initial diagnosis is made by cranial tomography, and magnetic resonance imaging is considered the gold standard.[3]

Immunohistochemical studies make it possible to complement the anatomopathological examination and direct therapeutic approaches. Among the most commonly used tumor markers in meningiomas are vimentin, epithelial membrane antigen (EMA), S-100 protein, carcioembryonic antigen, AE1AE3, glial fibrillary acid protein, progesterone receptor, and Ki-67. EMA expression is present in 90% of grade I meningiomas and only 75% of grade III meningiomas. Ki-67, a nuclear marker of cell proliferation, shows greater proliferative activity in grade III, with expression of 14.7% when compared to grades I and II, 3.8% and 7.2%, respectively.

Surgical resection is the gold standard treatment for meningiomas.[2] Simpson4 classified tumor resection as 5 grades and correlated it with the recurrence of these lesions. As the degree of Simpson resection advances, there is an increase in tumor recurrence.[4] Another relevant factor for this is the histological grade of the WHO, which determines that the higher the tumor gradation, the greater the increase in the recurrence rate.

Immunohistochemical markers have been studied in meningiomas to aid in diagnosis, treatment, and prognosis.[5] Among the predictors of tumor aggressiveness and recurrence are the proteins cyclin D1 and c-MYC. Both are directly related to the cell cycle, acting mainly during the transition from G1/phase S – accelerating the phase G1. Fu et al.[6] proved that the expression of cyclin D1 is related to tumor progression and increased risk of metastasis. Milenković et al.[7] showed a relationship between the expression of cyclin D1 and meningioma aggressiveness; however, Lee et al.[8] showed that it may be present in grade I meningiomas and related to tumor recurrence.

The c-MYC protein, encoded by the C-MYC oncogene, is regulated by external signals, including growth factors and extracellular matrix components, and by internal signals such as the cell cycle-activating machinery. The overexpression of this oncogene seems to induce chromosomal instability through the production of mitochondrial free radicals, which may participate in the suppression of antiangiogenic factors. C-MYC overexpression has been identified in CNS tumors, including brain gliomas and medulloblastoma.[9] However, studies correlating the expression of this protein in meningiomas are scarce.[10,11]

The development of new studies on the expression of cyclin D1 and c-MYC proteins in intracranial meningiomas may reflect on new forms of follow-up and treatment of these patients. More detailed knowledge of tumor behavior and recurrence has the potential to develop targeted therapies, minimizing the side effects of current treatment and optimizing quality of life.

The objectives of this study were to evaluate the expressions of cyclin D1 and c-MYC proteins in intracranial meningiomas and to correlate them with tumor aggressiveness and recurrence.

METHOD

The research was based on ethical precepts according to resolution No. 466/12 of the National Health Council and approved by the Research Ethics Committee of the institution (opinion 4,023,742). The identity of the participants was respected and the right to confidentiality was guaranteed. This is a retrospective, observational, cross-sectional study conducted at a university hospital, a reference in the care of patients with neurosurgical disease in Curitiba, PR, Brazil.

Patients and data collected

Patients diagnosed with intracranial meningioma and undergoing surgical treatment were selected. The initial search was performed based on data recorded in the file of patients operated on at the neurosurgery service. Then, data were collected and evaluated for eligibility and/or exclusion criteria.

The inclusion criteria were age over 18 years and histological diagnosis confirming meningioma. Exclusion included incomplete medical records or loss to outpatient follow-up in the postoperative period or technical problems in the preparation of immunostaining.

The initial sample totaled 54 patients. Three were excluded, 1 due to incomplete medical records, and another 2 did not have enough paraffin block samples to perform immunohistochemistry. Therefore, 51 patients were included. All underwent MRI and/or cranial CT in the immediate postoperative period and during outpatient follow-up, following the time interval recommended by the literature.[12] Next, the respective paraffin blocks were searched, and only those with a

tumor mass sufficient for immunohistochemistry with the markers cyclin D1 and c-MYC were selected.

Variables studied

The information was collected from the medical records and recorded in a table in the Microsoft Excel program. Data included gender, age (on the day of the surgical procedure), initial signs and symptoms at hospital admission, location of the tumor lesion according to MRI of the head (convexity, parasagittal or skull base, subclassified into anterior fossa, middle fossa and posterior fossa), degree of surgical resection according to the Simpson classification,[4] histological classification of meningioma, as proposed by the WHO.

The follow-up time was calculated in days from the difference between the date of the surgical procedure and the date of the last medical evaluation noted in the medical record. For follow-up analysis, the cases were classified as residual (incomplete tumor resection – Simpson's classification other than grade I), recurrence (tumor recurrence after complete resection of the lesion or enlargement of the residual lesion) and no disease (complete resection and absence of tumor recurrence, grade I). Disease-free survival time was defined as the interval in days between the date of the procedure and the end of follow-up (in those without recurrence) or until the date of diagnosis of a new expansive lesion suggestive of meningioma, based on cranial MRI. Those who died were kept in the overall follow-up count and the cause of death was also recorded. The end of the follow-up of cases was in March 2020.

Analysis of tumor markers

The tumor markers were analyzed using the tissue microarray (TMA) technique and then submitted to immunohistochemical studies and the preparation of multisample blocks. A manual device was used to prepare the Tissue Tek Quick-Array multisample blocks, which contained coupled tweezers with diameters between 1-3 mm, responsible for extracting the desired area. The clamp used was 2 mm. The complete technique for assembling the multisample blocks followed the usual standards for the method.

Immunohistochemistry was performed in the Ventana Bench Mark Ultra TM instrument with integrated 3-in-1 processing and the usual method of preparation was followed (Table 1).

TABLE 1 — Description of the primary antibodies with their manufacturers and dilutions

Biomarker	Primary antibody	Manufacturer	Dilution
Cyclin D1	SP4-R clone	Ventana	Pre-diluted
c-MYC	clone Y69	Ventana	Pre-diluted

The slides were analyzed by 2 different pathologists at different times using an Olympus CX31 microscope. Immunostaining was positive when the biomarker was present in the cell nucleus, and negative when it was not visualized in the cell distribution. The intensity of expression in the cell nucleus was subclassified into 3 scores (+/3+, ++/3+ and +++/3+). For correct interpretation, the cases were compared to the external control (mantle cell lymphoma for cyclin D1 and Burkitt's lymphoma for c-MYC), which presented a strong reaction (+++/3+). Cases that resembled external control in intensity were classified as +++/3+; those with a weak but detectable +/3+ reaction; and those with an intermediate-intensity reaction such as ++/3+.

Statistical analysis

Initially, a descriptive analysis of the data was carried out with simple and relative frequency estimation of the variables separately and according to the expression of the markers. Next, the differences between the expression proportions of the markers were verified with the chi-square test. The tests were considered significant when $p < 0.05$ and the analyses were performed using SPSS 21.0 (IBM, 2012).

RESULT

Descriptive analysis of the variables

Of the 51 patients, 37 were women (72.5%) and 14 were men (27.5%), giving a ratio of 2.6/1. The mean age was 53.5 years (19-84). Among the symptomatic patients, 52.9% had 1 symptom related to the disease. The presentation of 2, 3 and 4 symptoms were reported by 31.4%, 7.8% and 5.9%, respectively. One was asymptomatic (2%) at diagnosis. Headache was the most frequent symptom and was present in 74.5%.

Clinical semiology was normal in 41.2% of the cases. Motor deficit in the upper or lower limbs was present in 25.5% and cranial nerve alterations in 33.3%. Other clinical signs included appendicular sensory alterations (7.8%) and proptosis (1.9%).

Regarding the location of lesions on MRI of the skull, it was found that 53% of the meningiomas were located at the skull base, 33.3% in the convexity, and 13.7% in the parasagittal region.

According to the Simpson classification of surgical resection, 58.8% of the patients underwent complete resection (Simpson I) and 29.4% underwent complete resection followed by dural coagulation (Simpson II). Simple decompression with or without biopsy (Simpson V) was not identified in the sample (Figure 1).

Regarding the histological grade, 82.3% were classified as grade I; those in grade II and grade III represented 11.8% and 5.9%, respectively (Table 2).

The mean follow-up time was 798 days (13-2267) and the mean disease-free survival time was 816 days. Twenty-five patients (49%) were free of the disease; tumor recurrence was observed in 2 (3.9%) and residual lesion in 12 (23.5%). Twelve (23.5%) died. Causes of death included sepsis, systemic inflammatory response syndrome, upper gastrointestinal bleeding, and hemorrhagic stroke.

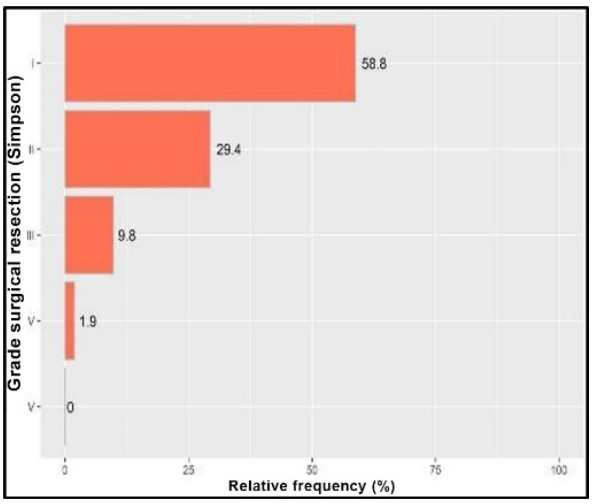

FIGURE 1 — Surgical resection of meningiomas

TABLE 2 — Histopathological classification of meningiomas

Grade (WHO)	Histological type	n	%
	Meningotelial	31	60,78
	Fibrous	1	1,96
	Transitional	4	7,84
Grade I n=42 (82.3%)	Psamomatous	3	5,88
	Secretary	1	1,96
	Angiomatous	1	1,96
	Metaplastic	1	1,96
Grade II	Atypical	5	9,80
n=6 (11.8%)	Chordoid	1	1,96
Grade III	Anaplastic	2	3,92
n=3 (5.9%)	Rhabdoid	1	1,96

Marker analysis

Cyclin D1 was found in all meningiomas, while c-MYC was found in only 17.7% of the cases (Table 3, Figures 2 and 3).

TABLE 3 — Expressions of cyclin D1 and c-MYC in meningiomas

Marker	Expression	n	%
Cyclin D1	Negative	0	0,0
	Weak	23	45,1
	Moderate	20	39,2
	Strong	8	15,7
c-MYC	Negative	42	82,3
	Weak	4	7,8
	Moderate	5	9,8
	Strong	0	0,0

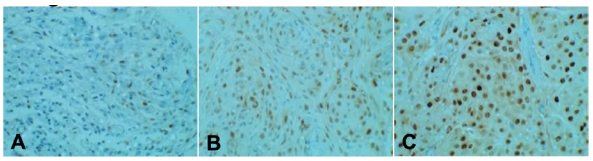

FIGURE 2 — Photomicrograph of intracranial meningioma with cyclin D1 expression: A) weak; B) moderate; C) Strong for the marker (400x magnification)

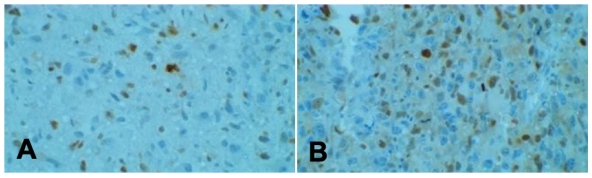

FIGURE 3 — Photomicrograph of intracranial meningioma with c-MYC expression: A) weak; B) moderate (400x increase)

Cyclin D1 analysis

She was positive in all cases. The characterization of the respective marker was based on the intensity of expression as weak, moderate and strong. There was a statistically significant association between cyclin D1 expression and tumor histological grade (p <0.001). Weak expression was more evident in grade I meningiomas and strong expression in 100% of grade III (Table 4).

TABLE 4 — Expression of cyclin D1 according to the histological grade of meningiomas

n		Weak			Moderate			Strong			p-value
		n	% col	% lin	n	% col	% lin	n	% col	% lin	
Grade (WHO)	I	22	95,7	52,4	17	85	40,5	3	37,5	7,1	<0.001
	II	1	4,3	16,7	3	15	50	2	25	33,3	
	III	0	0	0	0	0	0	3	37,5	100	

% col=percentage found in the column; % lin=percentage found in the line

The clinical outcome showed no correlation with cyclin D1 expression (p > 0.001, Table 5)

TABLE 5 — Cyclin D1 expression according to outcome

		Weak		Moderate		Strong		p-value
		n	% col	n	% col	n	% col	
Outcome	Death	7	30,4	3	15	2	25	0,631
	Relapse	0	0	1	5	1	12,5	
	Residual	6	26,1	5	25	1	12,5	
	No disease	10	43,5	11	55	4	50	

% col=percentage found in column

Analysis of the c-MYC marker

The analysis of c-MYC was performed by its expression in meningiomas and intensity of marker expression. There was a statistically significant association between its expression and the histological grade of meningiomas (p <0.001). This marker was negative in practically all grade I meningiomas (95.2%) and positive in all grade III meningiomas (Table 6).

TABLE 6 — Expression of c-MYC according to histological grade

		Negative			Positive			p-value
		n	% col	% lin	n	% col	% lin	
Grade (WHO)	I	40	95,2	95,3	2	22,2	4,7	<0.001
	II	2	4,8	33,3	4	44,4	66,7	
	III	0	0	0	3	33,3	100	

% col = percentage found in the column; % lin = percentage found in line

There was a statistically significant association between the intensity of c-MYC expression and the histological grade of meningiomas (p <0.001, Table 7). No expression of strong intensity was identified. Expression was moderate in all grade III meningiomas and weak in 50% in grade II.

TABLE 7 — Intensity of c-MYC expression according to histological grade

	Weak			Moderate			Strong			p-value
	n	% col	% lin	n	% col	% lin	n	% col	% lin	
I	40	95,2	95,2	1	25	2,4	1	20	2,4	<0.001
II	2	4,8	33,3	3	75	50	1	20	16,7	
III	0	0	0	0	0	0	3	60	100	

% col = percentage found in the column; % lin = percentage found in line

The clinical outcome of the patients under study did not show any correlation with the expression of the c-MYC marker (p >0.001, Table 8).

TABLE 8 — Expression of c-MYC according to outcome

		Negative		Weak		Moderate		p-value
		n	% col	n	% col	n	% col	
Outcome	Death	9	21,4	2	50	1	20	0,459
	Relapse	1	2,4	0	0	1	20	
	Residual	10	23,8	1	25	1	20	
	No disease	22	52,4	1	25	2	40	

% col=percentage found in column

DISCUSSION

Meningiomas are the most prevalent CNS tumors, with an incidence of approximately 9:100,000 inhabitants. Most of them affect the meninges of the intracranial space (80.6%). According to US data, approximately 35,000 new cases are estimated for 2021.[13]

In the present study, a higher incidence of intracranial meningiomas was found in women than in men (2:1), in accordance with the literature.[13,14] In agreement with other studies, the mean age was 53 years.[13-16]

Because it is a slow-growing tumor, symptoms can be insidious, and in some cases, patients may be asymptomatic at the time of diagnosis. In the sample evaluated, 1 patient was asymptomatic, which was considered an incidental diagnosis. Cases like this can represent 2.3%. In the study by Zouaoui et al.[17] the diagnosis of meningioma in asymptomatic patients was 9%.

Most of them complained of headache and dizziness Zouaoui et al.[17] also reported headache as the most common symptom in the study population (33.3%); Behbahani et al.[15] observed dizziness in 18% of the patients; Wu et al.[16] and Englot et al.[18] also reported seizures as one of the symptoms and correlated it with tumors located in the convexity due to the presence of vasogenic cerebral edema.

Cranial nerve abnormalities and motor deficit were the most common findings of the neurological physical examination, corresponding to 33.3% and 25.5%, respectively. Such alterations are more frequent in skull base lesions[16], mainly due to brainstem involvement.

Among the locations of meningiomas, it was observed that most were located at the base of the skull (53%). Behbahani et al.[15] and Milenkovic et al.[7] also observed a higher frequency of meningiomas in this location.

The degree of surgical resection is directly related to the possibility of recurrence of the lesion.[4] In the sample, most patients underwent complete resection of the lesion and its dural implantation – Simpson grade I.

Regarding the histological grade of the WHO, most of the tumors found were grade I, followed by grade II and, to a lesser extent, grade III.[13,17]

Most remained disease-free during postoperative follow-up with an average of 816 days, which agrees with published findings between 75% and 80% at 5 years.[19] Only 2 cases had recurrence and both underwent Simpson grade I resection, one of them with a transitional histological type (grade I) and the other atypical (grade II). There are several risk factors that influence tumor recurrence, including histological grade, expression of progesterone receptors, genetic alterations, bone involvement, and invasion of the piamater. Tumor recurrence was probably small because the vast majority had grade I tumors and underwent wide resection (Simpson grade I or II).

Death had a relative frequency of 23.5%. Sepsis accounted for 50%. This is probably due to the age of the patients, since the vast majority were elderly, or due to the involvement of the lower cranial nerves, promoting a greater chance of bronchial aspiration and airway infection, since 1 of them was young (25 years old) and had meningioma of the posterior fossa. Woehrer et al.[19] conducted a study evaluating causes of death in patients with non-malignant brain tumors and observed that 11.3% with grade I meningioma and 23% grade II died, and the main causes were due to other types of cancer and infection, which corroborates the data found here.

Immunohistochemistry is a widespread method in the scientific community that helps in diagnosis in oncology. This technique allows the disease to be correlated with prognosis by identifying enzymes, tumor-specific antigens, oncogenes, tumor suppressor genes, and cell proliferation markers. In meningiomas, the most commonly used tumor markers are vimentin, EMA, S-100 protein, CEA, AE1AE3, GFAP, CD34, the progesterone receptor, and Ki-67.5 The latter is disseminated as a marker that helps to define the severity of the injury and also the prognosis.[20]

Cyclin D1 and c-MYC are proteins that are directly involved in the cell cycle, promoting cell progression from phase G1 to phase S and are related to carcinogenesis in several types of tumors, including brain tumors.[6] Zeybek et al.[21] studied the presence of the cyclin D1 encoding gene (CCND1) in gliomas and meningiomas and it was observed that there is a relationship between this gene and the cause of these tumors. Overexpression of the c-MYC marker has also been identified in CNS tumors, including cerebral gliomas and medulloblastoma.[9,14] The investigation of

the c-MYC gene in meningiomas has already been the subject of 5 studies.[10,11,22-24,] and of these, 4 proved the presence of the gene in meningiomas. The one by Helseth et al.[22] was the first and only one where all 11 meningiomas samples did not have the c-MYC gene.

The study of these markers in meningiomas is still scarce and the study population is quite heterogeneous, since they do not always evaluate meningiomas in all histological grades. In this study, the expression of these markers in the different histological grades of meningioma was evaluated. Both are identified in the cell nucleus and the intensity of their expression was characterized as weak (+/3+), moderate (++/3+) and strong (+++/3+).

Cyclin D1 showed positive expression in all samples, and in grade I and II tumors the expression was predominant, weak and moderate, respectively. The intensity of expression in grade III meningiomas was strong in all cases. These findings agree with the research of Milenkovic et al.[7] who found cyclin D1 in 100% of meningiomas and observed that the expression of the marker was more intense in grade II and III meningiomas when compared to grade I tumors. Jiang et al.[25] also reported that the expression of the cyclin D1 marker is significantly higher in grade II and III meningiomas when compared to grade I; however, these authors did not disclose the percentage of tumors where the protein was identified.

Another 2 studies evaluated the presence of cyclin D1 in all grades of meningioma. Alama et al.[26] and Lee et al.[8] identified cyclin D1 in 81% and 97% of grade I meningiomas, respectively, and in 100% of grades II and III. El-Gewely et al.[27] evaluated the presence of cyclin D1 only in meningiomas grades I and II and also found this marker in 100% of the cases, similar to this study. Maxwell, Galanopoulos and Antoniades28 found the marker in 53% of their sample, which involved only grade I meningiomas. Gauchotte et al.[29] observed cyclin D1 positivity in 59% of meningiomas (50% of grade I tumors and 70% of grade II tumors) and concluded that the marker does not seem useful in the diagnostic and prognostic evaluation of meningiomas.

There was no association between the expression of the cyclin D1 marker and the outcome of the patients, as demonstrated by several authors.[25] Therefore, analyzing the expression of the cyclin D1 marker in meningiomas, it can be stated that the higher the tumor grade, the greater the intensity of cyclin D1 expression. Thus, this marker is a candidate for the immunohistochemical diagnosis of meningioma and, mainly, to help confirm the histological grade.

c-MYC was negative in most samples, being positive in only 17.7% of the cases. In grade I meningiomas, its presence was identified in only 2 samples (4.7%), in grade II tumors in 66.7% and in 100% in grade III tumors.

Detta et al.[10] found the c-MYC gene in 100% of their sample (n = 19), which involved meningiomas of all histological grades. Ng and Chen24 studied 51 meningioma samples and found c-MYC in 19% of the cases. Ongaratti et al.[14] analyzed 60 meningioma samples and the c-MYC marker was identified in 38%. However, Shivapathasundram et al.[30] identified it in all 11 cases of grade I meningiomas in their study. Nagashima et al.[31] also obtained results similar to those of the present study, since c-MYC was negative in all grade I meningiomas and positive in 100% of grade II and III tumors, suggesting that this marker is related to the malignancy of meningiomas. Tao et al.[32] reached a similar conclusion because they found the c-MYC marker in 95% of grade III meningiomas.[33] evaluated 26 meningioma samples and found the c-MYC marker in 27% of grade I tumors, 50% of grade II tumors, and 100% of grade III tumors.

When the intensity of marker expression and the histological type were correlated, it was observed that grade II meningiomas presented weak intensity for c-MYC in 50% of the cases; however, only 16% had moderate expression. All grade III meningiomas had moderate intensity of expression for c-MYC. None of the samples showed strong intensity for this marker.

Durant et al.[33] observed strong expression in only 2 cases, one of grade II meningioma and another grade III.[10] found the expression of strong intensity of the marker in 72% of their sample. Ongaratti et al.[14] considered that the expression of c-MYC was of strong intensity in 26% of the cases and significantly higher in grades II and III when compared to grade I.

The analysis of c-MYC in meningiomas demonstrates that its expression can correlate with the histological grade of these tumors, since its expression in moderate intensity is highly favorable to WHO grade III meningiomas. There was no association between c-MYC expression and the outcome of these patients, which is in agreement with the literature.[14]

Based on the data found in this research, the markers cyclin D1 and c-MYC help in the immunohistochemical diagnosis of meningioma. It can be suggested that the genesis of these tumors and, also, their progression are related to the acceleration of the cell cycle, more precisely in the transition from the G1 to S phase. The development of new studies involving other proteins or genes that are related to the cell cycle are important to elucidate tumor genesis and progression.

CONCLUSION

The cyclin D1 protein was expressed in all meningiomas samples and the c-MYC marker was expressed in 18% of the cases. The higher the histological grade of the tumor, i.[e.,] the more aggressive, the more intense the expression of these markers, but they did not correlate with the recurrence of meningiomas.

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