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Immunohistochemical Expression of MUC4, CD44, and Ki67/MIB1 in Different Meningioma Grades. A New Promise to Overcome the Chemoresistance Problem in Aggressive Meningioma

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Abstract

Background: MUC4 and CD44 have been addressed as major players in the progression and chemoresistance of several tumors.

Aim of Study: We aimed to elucidate the role of MUC4, CD44, and ki67 in meningiomas to detect if anti-cancer agents with mucin-depleting and proteolytic effects could help in overcoming chemoresistance in meningiomas.

Material and Methods: Fifty meningioma cases were immunohistochemically tested for CD44 and MUC4. In addition to grading of meningioma, Ki67/MIB 1 labeling index was evaluated.

Results: MUC4 and CD44 were expressed in 84% and 100% of our cases respectively. Significant correlation (p=0.007) was detected between meningioma subtypes and MUC4 intensity being highest in meningothelial and lowest in fibroblastic variant. Moreover, advanced meningioma grades were positively correlated with CD44 intensity (p<0.001) and Ki67/MIB1 labeling index (p<0.001). In addition, both CD44 and MUC4 immunohistochemical expression showed a significant positive association with Ki67/MIB 1 labeling index (p=0.011 and p=0.004) respectively.

Conclusion: MUC4 and CD44 are upregulated in advanced meningioma WHO grades II and III and correlated with a higher Ki67/MIB 1 labeling index. Subsequently, they can adversely influence the outcome and recurrence rate in meningioma and can be targeted by an agent with mucolytic and proteolytic effects helping in overcoming the common problem of chemoresistance in aggressive meningiomas.

Key Words: *CD44 – MUC4 – Ki67/MIB1 – Meningioma.*

Introduction

MENINGIOMAS are increasing in frequency in recent decades **[1]**, being widespread in Egypt, accounting for 25.6% among tumors of CNS and representing the 2nd most common tumor after glial neoplasms **[2]**. Three grades of meningiomas are identified. The majority of them are benign, WHO Grade I, with a favourable prognosis. Atypical meningiomas of grade II and anaplastic meningiomas of grade III show poor results **[3,4]**.

Complete surgical excision, including the involved dura, is the conventional treatment. Small tumors can be treated with radiosurgery, while big or previously treated tumors can be treated with fractionated radiation **[5]**. Pharmacotherapy involvement in meningioma is unclear, and there are no positive controlled clinical trials on which to base reliable recommendations. Even so, systemic salvage therapy for meningiomas is frequently considered for individuals who are no longer candidates for surgical resection or radiotherapy. Traditional cytotoxic drugs are frequently ineffective with only a partial response **[6]**.

Chemoresistance is primarily the result of treatment failures in most malignancies, which has been linked to tumor cell heterogeneity and the extracellular matrix. Many molecular changes have also contributed to chemotherapy resistance **[7]**. Resistance to mucins has been identified in several tumors including meningiomas. Mucins are split into two subfamilies based on their physiological and structural characteristics: Transmembrane mucins, which include MUC4, and secretory mucins **[8]**. Mucin provides tumor cells with a protective barrier against drug penetration and also accelerates survival pathways, chemotherapy resistance, metastasis, and accelerated replication **[9]**. CD44, a cell adhesion molecule, has been studied in meningiomas. It binds to the extracellular matrix molecule hyaluronan, which is involved in cell signalling and cell-matrix adhesion. It is found in nearly all human cells. Cell adhesion, migration, angiogenesis, proliferation, and inflammation are all regulated by it **[10]**. The intercellular matrix has both glycosidic and disulphide linkages that are susceptible to the action of certain agents such as Bromelain and Acetylcysteine (BromAc) **[11]**.

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Ki67/MIB 1 antigen is only expressed in the proliferative phase of the cell cycle and can be used as a way for expecting meningioma behavior [12]. So, in this work, we immunohistochemically studied MUC4, CD44, and ki67 expressions in different meningioma subtypes to detect if anti-cancer agents with mucin-depleting and proteolytic effects could help in overcoming the common problem of chemoresistance in meningiomas.

Material and Methods

This cross-sectional study included 50 meningioma cases collected retrospectively as paraffin-embedded tissue sections from Pathology Department, Kasr Al-Ainy School of Medicine, Cairo University from August 2022 to January 2023. Demographic data such as patients' age and gender were recorded from the revision of the patients' medical files (Table 1). Approval of the study from the institutional ethical committee was confirmed with a reference number: (N-1202023).

Histopathologic assessment:

Tumor sections of 3-4µm thickness were cut from each paraffin block and stained with Hematoxylin and Eosin. Two pathologists confirmed the diagnosis of meningioma and the histopathologic variant and WHO grade was assigned to each tumor according to the criteria of WHO classification of CNS tumor, 2016 [4].

Immunohistochemical assessment:

For immunohistochemical staining, three additional tumor sections of 3-4 thickness were re-cut from each paraffin block and mounted on charged slides. The examined antibodies were KI 67 monoclonal antibody (Clone MIB 1, Dako, United States of America), CD44 (#MS-668-R7, Lab Vision, United Kingdom), and MUC4 (abx 173628, Abbexa, United States of America). A fully automated immunohistochemical staining protocol was applied, Dako autostainer, link 48 was used and positive controls for each antibody were applied according to the manufacturer's protocol. The primary antibodies were suppressed as negative controls in the same tumor sections.

The nuclear positivity was calculated for tumor cells stained with the Ki67 antibody. The selection of a hot spot was performed and Ki67 nuclear immunostaining was examined in 100 nuclei and reported as a percentage.

Immunoreactivity for CD44 was assessed through detection of either membranous staining, cytoplasmic or both staining patterns and recorded as weak, moderate and strong when 0-5%, 5 up to 50% and more than 50% of examined tumor cells respectively stained positive for CD44 through immunohistochemical tests [13].

Examined meningioma cases were assigned positive for MUC4 if 1% f neoplastic cells displayed MUC4 cytoplasmic immunostaining. Tumor cells positive for MUC4 were counted in each section and assigned a final score ranging from 1 to 100% and the mean percentage was reported. Diffuse immunostaining was recorded if the positive neoplastic cells exceeded 50% [9]. A four-tiered grading score was performed to assess the intensity of immunostaining: (zero or negative: no staining), (one: mild intensity), (two: moderate intensity) and, (three: marked intensity) [14].

All results of the present study were enrolled in the SPSS software statistics program version 26. For quantitative data, the mean in addition to standard deviation was recorded. The frequencies and percentages were recorded for categorical data. The student *t*-test in addition to one-way ANOVA was used to compare different groups. The Chi-square (X^2) test or Fisher Exact test were used to compare non-numerical data. If p-value was not exceeding 0.05, a statistically significant relationship was reported.

Results

Fifty meningioma cases were enrolled in this study. Median age was 52 years, with 32 (64%) females and 18 (36%) males. Patients ranged in age from 25y to 71y, with a mean of 51±11.6y.

All cases were evaluated for MUC4, CD44, and ki67 expression by immunohistochemical staining.

MUC4 expression was positive in 84% (42/50) of the meningioma patients investigated. Diffuse staining (50% positive tumor cells) was seen in 44% (22/50) of cases, while 20 cases (40%) had 1-50% positive tumor cells. Strong intensity (marked staining, grasped with ease using low-power objective) was observed in 8 out of the 50 cases (16%) while 20 cases out of 50 cases (40%) showed moderate staining (adequately positive, moderately seen using low power objective); and 14 cases (28%) displayed weak staining (barely detectable, noticeable only with difficulty using low-power objective). On the other hand, no staining or staining of less than 1% of tumor cells was detected in 8 out of the whole 50 cases (16%). The meningothelial subtype represented 69% of positive tumor cells, and showed the highest mean percentage, while transitional, angiomatous and atypical

subtypes had a mean percentage of expression of 27%, 27.4%, and 26.4% consecutively. The lowermost mean percentage of positivity was seen in fibroblastic meningioma (1 %). Statistically, a significant relation was detected between the MUC4 intensity expression and meningioma subtype with a p-value of 0.007 (Fig. 1).

CD44 cytoplasmic and membranous immunostaining was seen in all examined cases and graded as being mild in 26 cases (52%), moderate in 10 cases (20%), and 14 cases (28%) marked. A statistically significant positive relationship was detected between expression of CD44 and grade of meningioma since marked expression was identified in 6 cases (60%) of the higher grades (II and III) meningiomas in comparison to 3 cases (7.5%) in Grade I (p-value <0.001) (Fig. 2).

The Ki67/MIB 1 labeling index ranged from 0.4% to 19%, averaging 6.5%. A significant positive correlation was detected between Ki67/MIB 1 labeling index and the meningioma grade (p-value <0.001). Statistically significant relationship was detected between Ki67/MIB 1 labeling index and tumor subtype with p-value=0.011 (Fig. 3).

Ki-67 proliferative index was found to have a significant positive connection with MUC4 expression and CD44 immunohistochemistry expression in meningioma patients with p-value was 0.004 and 0.011 respectively (Table 2).

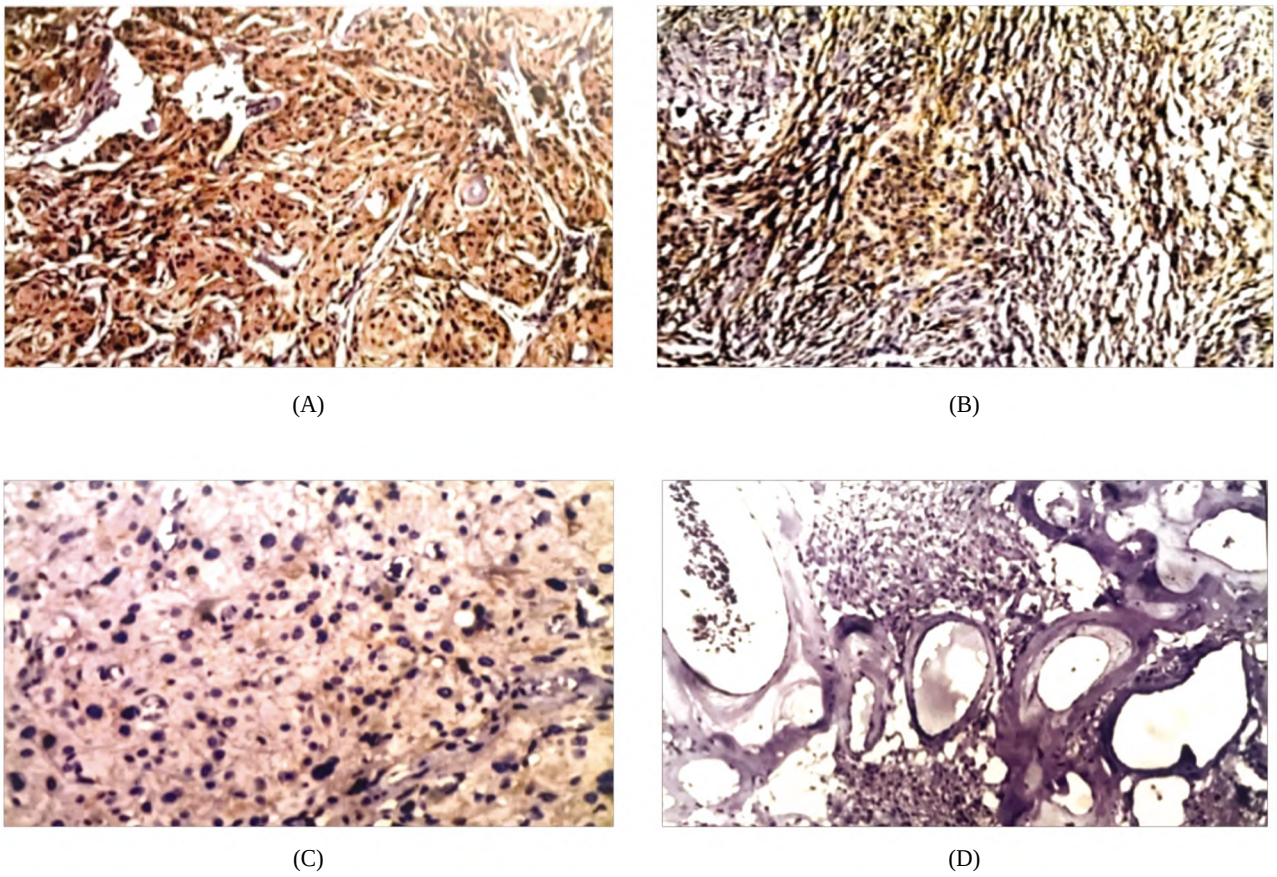
Table (1): MUC4, CD44, and ki67 expressions in relation to meningioma patients' clinicopathologic variables and histologic subtypes.

	MUC4 expression				p-value	CD44 expression			p-value	Ki-67	
	Positive			Negative		Weak	Moderate	Strong		Mean ±SD	p-value
	Strong	Moderate	Weak								
Age:											
50 22 (44%)	5 (23%)	8 (36%)	4 (18%)	5 (23%)	0.355	13 (59%)	6 (27.3%)	3 (13.7%)	0.256	6.8±8	0.835
>50 28 (56%)	3 (11%)	12 (43%)	10 (35%)	3 (11%)		13 (46.4%)	4 (14.3%)	11 (39.3%)		6.3±7.9	
Sex:											
Female 32 (64%)	6 (19%)	14 (44%)	8 (25%)	4 (12%)	0.653	17 (53.125%)	6 (18.75%)	9 (28.125%).	0.889	5.5±7.2	0.248
Male 18 (36%)	2 (11%)	6 (33%)	6 (33%)	4 (22%)		10 (55.56%)	4 (22.22%)	4 (22.22%)		8.6±8.9	
WHO Grade:											
Grade I 40 (80%)	8 (20%)	15 (38%)	9 (22%)	8 (20%)	0.174	34 (85%)	3 (7.5 %)	3 (7.5%)	<0.001*	2.9±2.2	<0.001*
Grade II, III 10 (20%)	0 (0%)	5 (50%)	5 (50%)	0 (0%)		0 (0%)	4 (40%)	6 (60%)		14.7± 10.45	
Histologic subtype:											
Meningothelial 12 (24%)	7 (58.3%)	4 (33.3%)	1(8.3%)	0 (0%)	0.007*	12 (100%)	0 (0%)	0 (0%)	0.109	2.9±2.2	0.011 *
Fibroblastic 6 (12%)	0 (0%)	0 (0%)	1 (16.7%)	5 (83.3%)		5 (83.3%)	0 (0%)	1 (16.7%)		3±2.1	
Transitional 17 (34%)	1 (6%)	6 (35%)	7 (41%)	3 (18%)		11 (64.7%)	4 (23.5%)	2 (11.8%)		2.8±1.9	
Angiomatous 4 (8%)	1 (25%)	2 (50%)	0 (0%)	1 (25%)		4 (100%)	0 (0%)	0 (0%)		2.9±2.2	
Psammomatous 1 (2%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)		1 (100%)	0 (0%)	0 (0%)		2.5	
Clear cell 2 (4%)	0 (0%)	2 (100%)	0 (0%)	0 (0%)		2 (100%)	0 (0%)	0 (0%)		10.4±9.8	
Atypical 7 (14%)	0 (0%)	3 (43 %)	4 (57%)	0 (0%)		0 (0%)	3 (42.9%)	4 (57.1%)		10.2±9.9	
Anaplastic 1 (2%)	0 (0%)	0 (0%)	1a (100%)	0 (0%)		0 (0%)	0 (0%)	1 (100%)		19.0	

*Statistical significance.

Table (2): Correlation of MUC4 and CD44 expressions with Ki-67 proliferative activity in studied meningioma cases.

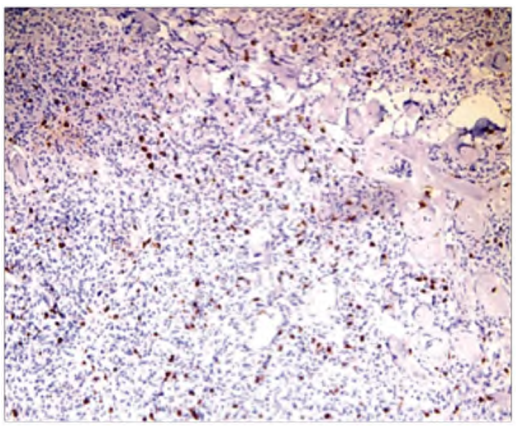
	Ki-67 Mean±SD	*p*-value
MUC4 expression:		
Positive	10.8±9.5	0.004
Negative	2.8±2.1	
CD44 expression:		
Mild	3.2± 2.4	0.011
Moderate	8.8±8	
Marked	11.3±11.5	



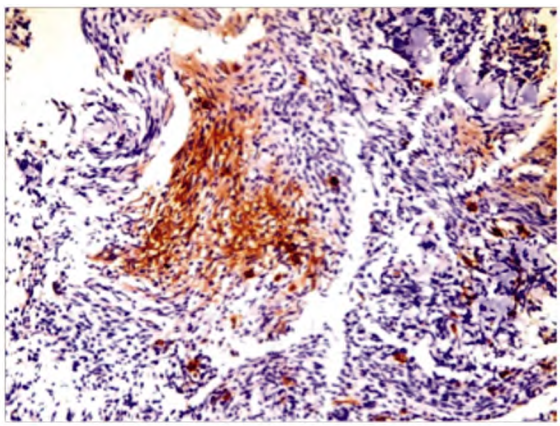
(A) (B)

(C) (D)

Fig. (1): Immunohistochemical expression of MUC4 in meningioma cases; A: Strong positive MUC4 expression in meningothelial meningioma (MUC4, original magnification x100), B: Moderate intensity of MUC4 in transitional meningioma (MUC4, original magnification x100), C: Weak expression of MUC4 in atypical meningioma (MUC4, original magnification x200), D: negative expression of MUC4 in a case of angiomatous meningioma (MUC4, original magnification x200)



(A)



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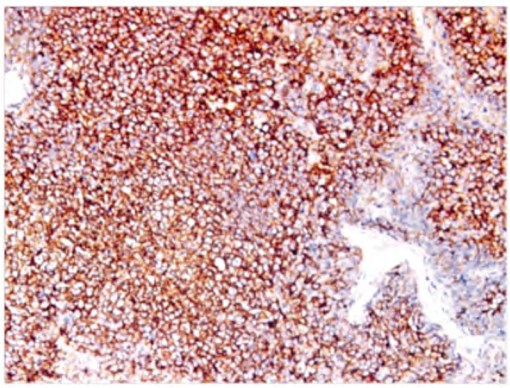

(C)

Fig. (2): CD44 immunohistochemical expression in meningioma; (A): Mild, (B): Moderate, (C): Marked (CD44, original magnification x 100).

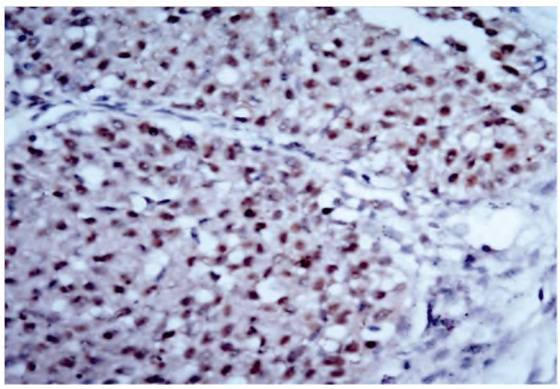

Fig. (3): ki67 nuclear expression in atypical meningioma (ki67, original magnification x400).

Discussion

Several prognostic factors with a negative impact on meningioma behaviour have been addressed including demographic factors such as younger age group and male sex, others related to poor Karnofsky performance status, higher WHO grades, and high proliferation index. Moreover, incomplete surgical resection and optic nerve infiltration have been linked to recurrent meningiomas. Thus, in spite of the clinical consensus that most meningiomas have benign behaviour, it is necessary to search for biomarkers and their related pharmaceutical therapy as a promising approach toward the improvement of meningioma outcomes **[15-17]**.

The present study included 50 meningioma cases with variable histopathologic variants and different meningioma grades evaluated for the expression of adhesion molecule CD44, transmembrane mucin MUC4, and Ki67 proliferation index through immunohistochemical techniques. In addition, the correlation of the previous aforementioned biomarkers expression with available clinicopathologic variables was performed.

In the current study, most of our studied meningioma cases (84%) showed positive MUC4 immunohistochemical expression and this was in concordance with Kong et al., 2020, Matsuyama et al., 2018 and Hasaneen et al., 2020 as 100%, 92.9% and 83.3% of their enrolled meningioma cases showed MUC4 positive immunohistochemical expression respectively **[18-20]**.

Kong et al., 2020 reported that highest positivity was reported in meningothelial and secretory meningioma (100%), followed by 97.8% in angioma-

tous meningiomas, 90.2% in atypical meningiomas and lowest in fibroblastic meningioma (13.5%) [18]. Similar figures were reported in our study as 100%; 12/12 of meningothelial and 7/7 of atypical meningiomas were positive for MUC4 followed by angiomatous meningioma (75%, 3/3) while only (1/6, 16.7%) of fibroblastic meningiomas were MUC4 positive.

In the present work, among different histopathologic variants, meningothelial meningioma had the highest MUC4 immunohistochemical mean percentage of positive tumor cells (69%) followed by angiomatous, transitional, and atypical meningioma; 27.4%, 27%, and 26.4% respectively. On the other hand, fibroblastic meningioma showed 1% only MUC4 positive tumor cells. In agreement with our results, Matsuyama et al., 2018, reported diffuse and constant MUC4 immunostaining in meningothelial and angiomatous meningiomas, while it was restricted to less than 5% of tumor cells in fibroblastic meningioma subtype [19].

The pattern of MUC4 immunostaining in our study was diffuse in 44% and focal in 40% of our studied meningioma cases. Moreover, 16%, 40% and 28% of the enrolled meningioma cases showed strong, moderate, and weak MUC4 cytoplasmic immunostaining respectively.

In the same context, Hasaneen et al., 2020 reported similar figures as among their MUC4 positive meningioma cases, 36% showed a score 3+, 40% showed a score of 2+, and 24% cases showed a score of 1+ [20].

Moreover, a statistically significant correlation was detected in our study between MUC4 immunostaining intensity and different meningioma histopathologic variants (p-value=0.007).

All examined meningioma cases (50/50, 100%) in our work displayed CD44 cytoplasmic and membranous immunostaining. Lower figures were reported by Lewy-Trenda et al., 2004 as (26/61, 42.6%) of their examined meningioma cases were positive for CD44 immunohistochemical expression [21].

Variable grades of CD44 immunostaining were observed in the current study as mild, moderate and marked in 52%, 20%, and 28% of studied meningioma cases respectively.

A significant positive correlation was detected in the present study between expression of CD44 and grade of meningioma since marked expression was identified in 6 cases (60%) of the higher grades (II and III) meningiomas in comparison to 3 cases (7.5%) in Grade I (p-value <0.001). In agreement with our study, Lewy-Trenda et al., 2004 reported a shift towards higher CD44 expression in WHO grade II meningioma (70%) compared to WHO grade I meningioma (37.3%) with statistical significance (p-value <0.001) [21]. In the same context, Lewy-Trenda et al., 2004 stated that diffuse strong membranous CD44 immunostaining was detected in WHO grade II meningiomas, supporting the potential role of mutated CD44 glycoprotein in invasiveness and proliferation of tumor cells [21].

Moreover, Kamamoto D et al., 2019 stated that in a multivariate analysis, CD44 expression in meningioma was associated with shorter progression-free survival (PFS), (p-value=0.0563), as was reported by the classic WHO grade and Simpson grade (p-value=0.0166 and p-value=0.0333, respectively) [22].

The proliferative activity of tumor cells was examined in our studied meningioma cases by Ki-67 labelling index and ranged from 0.4% up to 19% with an average of 6.5% with a statistically significant shift towards a higher proliferation index in advanced grades. Solanke et al., 2020 reported figures in a similar range as Ki 67 labelling index ranging from 1 % to 12% in their enrolled meningioma cases with median of 4% in WHO grade I meningiomas and 7% in WHO grade II meningiomas with a statistical significance between both grades [23]. Higher figures were reported by Menger et al., 2017 as their mean Ki-67 immunostaining score was 9.75% (ranging from1% to 48%) [24]. This may be affected by the enrolment of recurrent meningiomas in their study.

Two recent studies performed by Nagahama et al., 2021 and Liu et al., 2020 also supported our results as higher Ki-67 expression levels were associated with meningioma recurrence and lower survival rates respectively [15,25]. The aforementioned meta-analysis done by Liu et al., 2020 also stated that a ki67 cut off value (>4%) is more appropriate for expecting meningioma survival and outcome. Liu and his colleagues also recommended testing Ki-67 proliferation index in all meningiomas for the planning of proper treatment strategy and predicting the prognosis and selection of cases in need of strict follow-up [15].

A significant positive correlation between Ki-67 proliferative index and both the transmembrane mucin MUC4 and CD44 adhesion molecule immunohistochemical expression with p-value=0.004 and 0.011 respectively was reported in the investi-

gated meningioma cases supporting the impact of both MUC4 and CD44 on proliferation and aggressiveness of tumor cells.

In the highlights of the above results, we concluded that both biomarkers MUC4 and CD44 are widely expressed and associated with higher grades of meningiomas and can adversely affect the prognosis and recurrence rate and they can be targeted by an agent with mucolytic and proteolytic effects helping in overcoming the common problem of chemoresistance in aggressive meningiomas.

The combination of immunohistochemical expression of both aforementioned biomarkers was correlated with higher proliferative activity of tumor cells as demonstrated by Ki67 immunostaining addressing them as poor prognostic indicators and potential targets for future application of pharmaceutical therapy in aggressive meningiomas.

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التعبير الكيميائى الهيستولوجى المناعى لـ MUC4 و CD44 وKi67/MIB1 فى درجات مختلفة من الورم السحائى. وعد جديد للتغلب على مشكلة المقاومة الكيميائية

يعتبر كلا من MUC4وCD44 لاعبين رئيسيين فى تطور ومقاومة العديد من الأورام للعلاجات الكيميائية. لقد توضيح دور MUC4 وCD44 وki67 فى الأورام السحائية لاكتشاف ما إذا كانت العوامل المضادة للسرطان ذات التأثيرات المستنفدة للميوسين والمحللة للبروتين يمكن أن تساعد فى التغلب على المقاومة الكيميائية فى الأورام السحائية. تم اختبار فى CD44 و MUC4 مناعياً فى خمسين حالة من حالات الورم السحائى. بالإضافة إلى تصنيف الورم السحائى، تم تقييم مؤشرKi67/MIB1. تم التعبير عن MUC4 وCD44 فى 84% و 100% من حالاتنا على التوالى. تم الكشف عن ارتباط كبير (p=0.007) بين الأنواع الفرعية للورم السحائى شدة MUC4 وهى الأعلى فى النوع السحائى والأدنى فى النوع الليفى. علاوة على ذلك، ارتبطت درجات الورم السحائى المتقدم بشكل إيجابى مع شدة CD44 (p<0.001) ومؤشرKi67/MIB1 (p<0.001). بالإضافة إلى ذلك، أظهر كل من التعبير الكيميائى المناعى CD44 وMUC4 ارتباطاً إيجابياً مهماً مع مؤشر Ki67/MIB1 على التوالى.

فى الختام، تم استنتاج وجود MUC4 وCD44 فى الورم السحائى المتقدم من الدرجة الثانية والثالثة لمنظمة الصحة العالمية ووجودهما مرتبط بمؤشر Ki67/MIB1 أعلى وبالتالى، يمكن أن تؤثر سلباً على معدل التكرار فى الورم السحائى ويمكن استهدافها بواسطة عامل له تأثير كمذيب للمخاط ومحلل للبروتين والذى قد يساعد فى التغلب على المشكلة الشائعة المتمثلة فى المقاومة الكيميائية فى الأورام السحائية العدوانية.