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RELATIONSHIP BETWEEN EXPRESSION CLUSTER OF DIFFERENTIATION 44 (CD44) WITH MITOSIS, GRADE AND BRAIN INVASION IN MENINGIOMA

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ABSTRACT

Meningioma is the most common brain tumor. Most cases are benign with slow growth. WHO grade 2 and 3 meningiomas have a more aggressive behavior and with high recurrence. CD44 is a cell surface glycoprotein that has an important role in proliferation, cellular adhesion, migration, and angiogenesis. This study is a cross sectional study with a sample of 40 cases of meningioma at Prof. Dr. I.G.N.G. Ngoerah Hospital in 2019-2022 consisting of 20 grade 1 cases, 14 grade 2 cases, and 6 grade 3 cases. Clinical and radiological data were obtained from SIMRS. Hematoxylin-Eosin slide re-evaluation was performed to assess mitosis and tumor invasion into the brain. CD44 expression was evaluated by immunohistochemistry. Descriptive analysis to determine the frequency of the characteristics of the study subjects and chi square analysis to analyze the relationship between CD44 expression with mitosis, grade, and brain invasion. Significance was determined at $p < 0.05$. The results obtained were 25 cases (62.5%) aged in the fourth decade, 30 (75%) cases were female, 24 (60%) cases were located in non-convexity, 26 (65%) cases with size <6 cm, 20 (50%) cases grade 1, 7 (17.5%) cases showed brain invasion and 26 (65%) cases had mitosis <4/10 LPB. CD44 expression was weak in 11 (27.5%) cases, moderate expression in 17 (42.5%) cases and strong expression in 12 (30%) cases. In bivariate analysis, there was a significant association between CD44 and mitosis ($p = 0.011$), grade ($p = 0.004$), and brain invasion ($p = 0.023$). In conclusion, there is a significant association between CD44 expression with mitosis, grade, and brain invasion in meningioma.

Keywords: meningioma., CD44., mitosis., grade., brain invasion.

INTRODUCTION

Meningiomas are tumors that originate from leptomeningen meningothelial (arachnoid) cells, which can occur along the arachnoid site and attach to the inner surface of the duramater[1]. Meningioma is the most common primary brain tumor with a prevalence of 27%, with an incidence rate of 6 per 100,000 population. At Cipto Mangunkusumo Hospital Jakarta, meningiomas account for 45.1% of all brain tumors[2]. Research conducted at the Prof. Dr. I.G.N.G Ngoerah Central General Hospital in 2014-2018 explained that meningioma was the brain tumor with the highest incidence of 107 cases[3].

The histology grade of meningioma is determined based on the histology type of the tumor, proliferation index and invasion of the brain parenchyma[4]. Meningioma, WHO grade 1 is found in 80.5% of all meningiomas and has a benign and slow-growing histology[5]. WHO grade 2 and 3 meningiomas comprise 17.7% and 1.7% of meningiomas respectively, and have atypical to malignant histology features indicating a more aggressive clinical course[6]. Grade using mitosis and invasion into the brain parenchyma is associated with risk of recurrence and overall survival, as well as therapeutic strategies[7,8]. The presence of increased mitosis is associated with lower recurrence and PFS and is an independent predictive factor for recurrence and is an independent predictive factor for transformation to high grade in grade 1 meningiomas[9,10,11].

CD44 is a glycoprotein that plays an important role in proliferation, cellular adhesion, migration, and angiogenesis. CD44 is assumed to be associated with tumor invasion as well as metastatic ability[12,13]. Some malignancies that have been known to be associated with CD44 are pancreatic cancer, breast cancer, prostate cancer, SCC of the head and neck and gastrointestinal cancers[14]. In meningiomas, extensive expression of grade 2-3 CD44 may reflect a more invasive tendency of the neoplastic cells to the surrounding tissues (dura, bone and brain parenchyma). CD44 expression is associated with the grade of meningioma [12, 15]. CD44 expression can be a predictor of aggressiveness and has a trend for progression-free survival (PFS). [16].The purpose of this study was to determine whether there is an association between CD44 expression with mitosis, grade, and brain invasion in meningioma.

MATERIALS AND METHODS

Research Subject

This study used a cross-sectional design. The sample size of this study was 40 cases of meningioma that had been

histopathologically examined at the Anatomical Pathology Laboratory of Prof. dr. I.G.N.G. Ngoerah Hospital, Denpasar from January 1, 2019 to December 31, 2022 who met the inclusion criteria set by the researcher. This study has received permission from the Research Ethics Commission of the Faculty of Medicine, Udayana University / RSUP Prof. dr. I.G.N.G. Ngoerah Denpasar with ethical eligibility letter number 1840/UN14.2.2.VII.14/LT/2023 and has been given permission by RSUP Prof. dr. I.G.N.G. Ngoerah with letter number DP.04.03/XIV.2.2/43837/2023.

Inclusion criteria used were patients with intracranial and intraspinal tumors, diagnosed with meningioma by histopathological examination of resection material. Complete clinical data including age, gender, tumor size and tumor location listed on medical record data, as well as paraffin blocks in good condition and still contain sufficient tumor tissue.

Clinicopathologic Variables

Meningioma is a tumor originating from leptomeningen meningothelial (arachnoid) cells, which can occur along the arachnoid site and attach to the inner surface of the duramater[1]. The criteria for the diagnosis of meningioma is based on the histopathological picture with Hematoxylin-Eosin stain. Data of meningioma cases were obtained from medical records through medical record of Prof. dr. I.G.N.G. Ngoerah Hospital Denpasar.

Mitosis was determined using the number of mitoses obtained from histopathological examination using Hematoxylin-Eosin smears. The number of mitoses was categorized into: <2.5 mitoses/mm^2 (equivalent to <4/10 LPB) and≥ 2.5 mitoses/mm^2 (equivalent to≥ 4/10LPB).

Brain invasion is the presence of neoplastic meningothelial cells invading the brain parenchymal tissue as determined by histopathological examination using Hematoxylin-Eosin smears. Brain invasion was defined as positive and negative brain invasion.

Grade of meningioma is determined based on histology type or number of mitoses or morphological criteria or the presence of anaplasia. Grade is grouped into 2 categories namely grade 1 and grade 2/3.

Immunohistochemical staining

CD44 expression was evaluated by immunohistochemical examination using CD44 (SPM521) Mouse Monoclonal antibody. The pulse value was determined using a quantitative method. The pulses were assessed on the cell membrane and/or cytoplasm of tumor cells. Assessment criteria were based on the percentage of cells that were stained. CD44 expression was categorized into 3 categories: weak, moderate and strong. Weak expression was determined if 0-5% of tumor cells were stained; moderate if 6-50% of tumor cells were stained, and strong if >50% of tumor cells were stained[15]. CD44 expression was determined using immunohistochemical staining, using an Olympus CX23 LED binocular light microscope with a magnification of 40-400 times performed by the researcher and 2 anatomical pathology specialists independently and without prior knowledge of clinicopathological information. If there was a difference between the researcher and the 2 anatomical pathologists, a consensus agreement was made.

Statistical analysis

Descriptive analysis is the frequency of the characteristics of the study sample including age group, gender, tumor location, tumor size, mitosis, grade, tumor invasion and CD44 expression. Chi square analysis analyzed the relationship between CD44 expression with mitosis, grade and brain invasion. The significance threshold (α) was determined at a level of significance of $p < 0.05$. Data were processed using the Statistical Package for the Social Sciences (SPSS) 26.0 program for Windows.

RESULTS

The research samples were paraffin blocks from patients with meningioma cases who had undergone histopathological examination at the Anatomical Pathology Laboratory of Prof. Dr. I.G.N.G. Ngoerah Denpasar Hospital, from January 1, 2019 to December 31, 2022. During this period there were 160 cases that met the inclusion and exclusion criteria set by the researcher. Grade 2 and 3 meningioma cases were used in total, namely 14 cases of grade 2. And 6 grade 3 cases. A total of 20 grade 1 cases were selected consecutively. The characteristics of the study sample based on age obtained the youngest age of 16 years and the oldest age of 66 years, the median age at the age of 47 years and the mean age of 46.29 ± 9.163 years. The number of cases based on several clinicopathological parameters is presented in Table 1. Figure 1 shows a graph of the number of cases by age group while Figure 2 shows the results of H-E smears of anaplastic meningioma with brain invasion and Figure 3 shows CD44 immunohistochemistry.

Table 1 Number of cases on several pathological parameters

Sample characteristics		Frequency	Percentage (%)
Age (years)	11-20	1	2,5
	21-30	2	5,0
	31-40	3	7,5
	41-50	25	62,5
	51-60	7	17,5
	61-70	2	5
Gender	Male	10	25
	Female	30	75
Tumor Location	Convexity	16	40
	Falx&parasagital	8	20
	Posterior fossa	2	5
	Intraorbital	3	7,5
	Sphenoid wing	5	12,5
	Suprasellar	5	12,5
	Spinal	1	2,5
Tumor Size (cm)	<6	26	65
	≥6	14	35
Mitosis (LPB)	<4/10	26	65
	≥4/10	14	35
Grade	1	20	50
	2/3	20	50
Invasion	Negative	33	82,5
	Positive	7	17,5
CD44 Expression	Weak	11	27,5
	Medium	17	42,5
	Strong	12	30

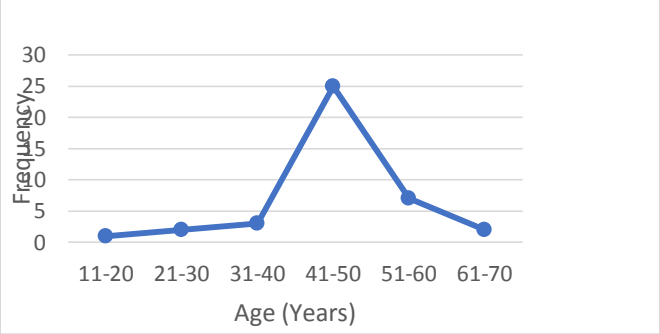

Image 1. Graph of the number of cases by age group

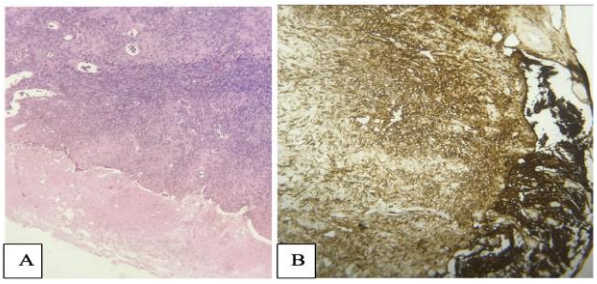

Image 2 Anaplastic meningioma, WHO grade 3 CNS with Brain Invasion
A. 100x magnification (HE), B. 100x magnification (CD44)

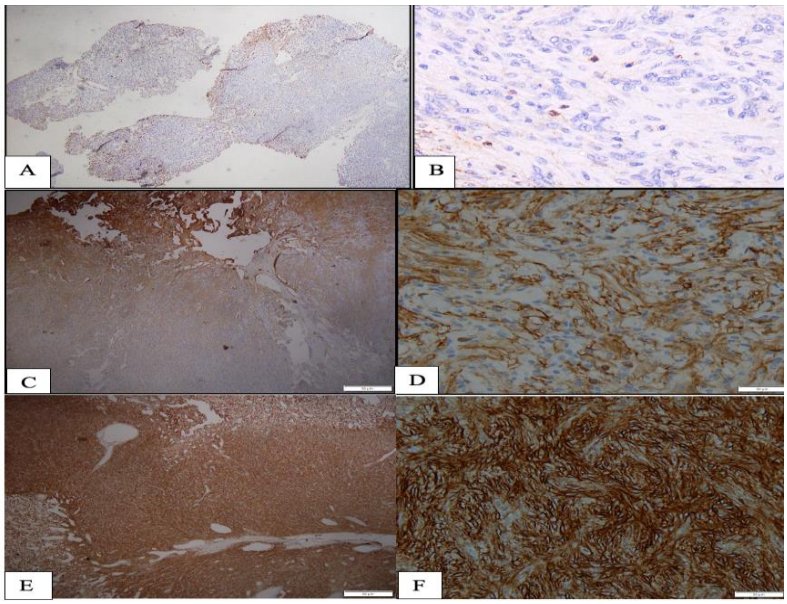

Figure 3 Immunohistochemical expression of CD44 in meningiomas. A-B CD44 expression is weak. Only 0-5% of tumor cells are stained. Magnification 40x, 400x C-D. CD44 expression is moderate. 6-50% of tumor cells are stained. 40x, 400x magnification
E-F. CD44 expression is strong. >50% of tumor cells are stained. 40x magnification, 40

Table 2 shows the analysis of the relationship between grade and several clinicopathological parameters. The table shows that grade was not associated with age, gender, tumor location and tumor size ($p>0.05$). Grade was associated with mitosis and invasion ($p<0.05$).

Table 3 shows that in meningioma cases at Prof. dr. I.G.N.G. Ngoerah Denpasar Hospital from 11 cases that showed weak CD44 expression, all (100%) had mitosis <4/10 LPB. In cases with moderate CD44 expression, 10 cases (58.8%) showed mitosis <4/10 LPB and 7 cases (41.2%) had mitosis≥ 4/10 LPB. In cases with strong CD44 expression, 5 cases (41.7%) had mitoses <4/10 LPB and 7 cases (58.3%) had mitoses≥ 4/10 LPB. In the chi-square analysis to assess the relationship between CD44 expression and mitosis, the p value = 0.011 means that there is a statistically significant relationship between CD44 and mitosis.

Table 4 shows that in meningioma cases at Prof. Dr. I.G.N.G. Ngoerah Denpasar Hospital, out of 11 cases that showed weak CD44 expression, 10 cases (90.9%) were grade 1 and 1 case (9.1%) was grade 2/3. In cases with moderate CD44 expression, 7 cases (41.2%) were grade 1 and 10 cases (58.8%) were grade 2/3. In cases with strong CD44 expression, 3 cases (25%) were grade 1 and 9 cases (75%) were grade 2/3. In the chi-square analysis to assess the relationship between CD44 expression and grade, the p value = 0.004 means that there is a statistically significant relationship between CD44 expression and grade.

Table 5 shows that in meningioma cases at Prof. Dr. I.G.N.G. Ngoerah Denpasar Hospital, out of 11 cases that showed weak CD44 expression, all (100%) had negative brain invasion. In cases with moderate CD44 expression, 15 cases (88.8%) showed negative brain invasion and 2 cases (11.8%) had positive brain invasion. In cases with strong CD44 expression, 7 cases (41.7%) had negative brain invasion and 5 cases (41.7%) had positive brain invasion. In the chi-square analysis to assess the relationship between CD44 expression and invasion, the p value = 0.023 means that there is a statistically significant relationship between CD44 and tumor invasion to the brain.

Table 2 Relationship between grade and some clinicopathological parameters

	Variables	Grade		p
		1	2 and 3	
Age (years)	11-20	0 (0%)	1 (5%)	0,871
	21-30	1 (5%)	1 (5%)	
	31-40	1 (5%)	2 (10%)	
	41-50	14 (70%)	11 (5%)	
	51-60	3 (15%)	4 (20%)	
	61-70	1 (5%)	1 (5%)	
Gender	Male	3 (15%)	17 (85%)	0,144
	Female	7 (35%)	13 (65%)	
Tumor	Convexity	6 (30%)	10 (50%)	0,791
Location	Falx and parasagittal	5 (25%)	3 (15%)	
	Posterior fossa	1 (5%)	1 (5%)	
	Intraorbital	2 (10%)	1 (5%)	
	Sphenoid wing	3 (15%)	2 (10%)	
	Suprasellar	2 (10%)	3 (15%)	
	Spinal	1 (5%)	0	
Tumor Size	<6 cm	14 (70%)	6 (30%)	0,507
	≥6cm	12 (60%	8 (40%)	
Mitosis	<4/10Lpb	20 (100%)	0	**0,000**
	≥4/10Lpb	6 (30%)	14 (70%)	
Invasion	Negative	20 (100%)	0	**0,004**
	Positive	13 (65%)	7 (35%)	

Table 3 Relationship between CD44 expression and mitosis in meningiomas at Prof. Dr. I.G.N.G. Ngoerah Hospital Denpasar

CD 44 Expression	Mitosis		Total	p
	<4/10 LPB	≥4/10 LPB		
Weak	11 (100%)	0 (0%)	11 (100%)	0,011
Medium	10 (58,8%)	7 (41,2%)	17 (100%)	
Strong	5 (41,7%)	7 (58,3%)	12 (100%)	

Significance cutoff value at $p < 0.05$

Table 4 Relationship between CD44 expression and Grade in meningioma at Prof. Dr. I.G.N.G. Ngoerah Hospital Denpasar

CD 44 Expression	Grade		Total	p
	1	2/3		
Weak	10 (90,9%)	1 (9,1%)	11 (100%)	0,004
Medium	7 (41,2%)	10 (58,8%)	17 (100%)	
Strong	3 (25%)	9 (75%)	12 (100%)	

Significance cutoff value at $p < 0.05$

Table 5 Relationship between CD44 expression and brain invasion in meningioma at Prof. Dr. I.G.N.G. Ngoerah Hospital Denpasar

CD 44 Expression	Brain invasion		Total	p
	Negative	Positive		
Weak	11 (100%)	0	11 (100%)	0,023
Medium	15 (88,2%)	2 (11,8%)	17 (100%)	
Strong	7 (58,3%)	5 (41,7%)	12 (100%)	

Significance cutoff value at p

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DISCUSSION

The incidence of meningioma increases with age, with the median age at diagnosis being 66 years. The incidence rate in patients aged≥ 40 years was 18.69/100,000 and age 0-19 years was 0.16/100,000. Meningiomas occurred in patients aged≥ 40 years in 43.6% of all CNS tumors[5]. Research conducted at the Prof. Dr. I.G.N.G Ngoerah Central General Hospital in 2014-2018 explained that meningioma is a brain tumor with the highest incidence, 54.5% of meningioma cases are in the age range of 40-49 years. Another study at Dr. Hasan Sadikin Bandung Hospital in the period 2010-2013, 39% of cases were in the age range of 41-50 years. The same thing was found in this study, where the median age was 47 years old and 25 (62.5%) cases were in the fourth decade (41-50 years). This could be due to the complex etiopathogenesis. Although most meningiomas occur sporadically, some cases are associated with certain risk factors including alcohol, obesity, occupational exposure to ionizing radiation, radiotherapy and hormonal imbalances[17]. Most cases of meningioma are benign tumors that grow slowly, so it takes a long time to cause complaints or symptoms and often occurs in old age. Many cases of meningioma are found incidental findings at autopsy (asymptomatic)[18].

In this study, the distribution of cases based on gender was found to be mostly female, as many as 30 (75%) cases, much higher than in men with a ratio of 3:1. The high incidence in females is related to hormonal factors. A number of observations suggest a role for sex hormones in meningioma tumorigenesis. The incidence of meningioma is 2 times greater in women than men. Meningiomas have also been reported to have increased growth during pregnancy and the luteal phase of the menstrual cycle. In addition, the incidence of meningiomas is increased in breast cancer patients. Although estrogen and androgen receptors are both found on meningiomas, progesterone receptor expression is most commonly observed. Progesterone receptors are expressed in 81% of women and 40% of men with meningiomas, and are minimally present in normal arachnoidal cells. Progesterone receptor expression is highest in benign meningiomas (50%-80%), and is inversely related to tumor proliferation and grade [5].

In this study, meningiomas located in the convexity area were found in 16 cases (40%). Some studies mentioned 20-37% of meningiomas are found in the convexity area. The location of convexity tumors is interesting because some studies mention that these tumors have a high risk of post-surgical epilepsy of 11-25%, and have a twice greater risk of recurrence[19,20]. However, along with technological advances and therapeutic modalities, radiosurgery has a very good impact in reducing the risk of recurrence. Recurrence in convexity meningioma is related to WHO grade and Simpson Grade[21]. In Simpson Grade 1, macroscopic resection with complete removal of tumor, dura and bone, if the tumor arises from the dural venous sinus wall, then sinus resection surgery is required. Simpson Grade 2 when macroscopically, complete tumor resection and extension to the dura. Simpson Grade 3, when macroscopically complete tumor removal. Simpson Grade 4 when partial resection, leaving intradural tumor in situ. Simpson Grade 5 decompression with/without biopsy. Simpson Grade is no longer significant and should be replaced with a grading scale with postoperative MRI that grades gross total resection (GTR) with subtotal resection (STR) and then divides STR into more or less than 4-5 cm^3, which is combined with modern molecular-based stratification for recurrence risk[22].

This study found that 26 (65%) cases had mitoses <4/10 LPB. While 14 (35%) cases had mitosis as much as≥ 4/10 LPB. Mitosis is one of the criteria used to determine the grade of meningioma. Mitosis included in the diagnosis criteria that has been set as a standard in determining WHO grade is at WHO grade 1 is mitosis no more than 4/10 LPB. WHO grade 2 must meet the following criteria: increased mitosis (4-19/10 LPB). At WHO grade 3 must meet the following criteria: mitosis≥ 20/10 LPB[23].

In bivariate analysis, there was a statistically significant relationship between CD44 expression and mitosis (p = 0.011). In cases with weak CD44 expression, all cases (100%) had mitosis <4/10 LPB. In cases with moderate CD44 expression, 10 cases (58.8%) showed mitosis <4/10 LPB and 7 cases (41.2%) had mitosis≥ 4/10 LPB. In cases with strong CD44 expression, 5 cases (41.7%) had mitosis <4/10 LPB and 7 cases (58.3%) had mitosis≥ 4/10 LPB. No study has examined the relationship between CD44 expression and mitosis in meningioma. An increase in mitosis is associated with recurrence and PFS[9]. Mitosis is an independent predictive factor for transformation to high grade in grade 1 meningioma. These results showed consistency in multivariate analysis[10,11].

There are several molecular mechanisms associated with CD44 activation in promoting proliferation in several types of tumors. In chronic myeloid leukaemia, the role of CD44 in proliferation is through the regulation and activation of the Wnt/β -catenin signaling pathway. Downregulation of CD44 can decrease the expression ofβ -catenin and increase the phosphorylation ofβ -catenin. This causes inhibition in cell proliferation. In pancreatic intraepithelial neoplasia and pancreatic ductal adenocarcinoma, CD44 has an important role in upregulating the expression of EMT biomarkers namely Snail1 and Zeb1. CD44 inhibition in pancreatic ductal adenocarcinoma cells significantly impaired cell proliferation. In lung adenocarcinoma, CD44 is known to have an important function in the activation of the KRAS oncogenic pathway, which in turn leads to tumor proliferation and survival. In breast carcinoma, CD44 also has a very important role in regulating proliferation, invasion and migration by regulating the expression of c-Src, a key regulator in the MAPK, PI3K and STAT

signaling pathways. In addition to the above, the role of CD44 in cell proliferation in thyroid carcinoma cells is seen in the translocation of CD44 to the nucleus and produces CD44 intracellular domain (CD44-ICD). CD44-ICD can bind to cAMP response element-binding protein tarnscription factor (CREB-TF). The binding will increase the activity of cyclin D1. Cyclin D1 is a transcription and cell proliferation protein[24]. The pathological mechanism that can explain the role of CD44 in the progressivity of meningioma tumors is the interaction between CD44 and specific ligands, one of which is HA, which can induce several signaling pathways of tumor cell development in various malignancies. One of them is oncogenic pathways such as mitogen activation protein kinases (MAPK) and PI3 kinases/act pathways that can promote tumor cell proliferation, survival, migration, invasion, and chemoresistance[25].

The grade of meningioma is associated with the risk of recurrence and overall survival and influences the choice of therapy. Grade meningiomas are classified into WHO grade 1, 2 and 3. WHO grade 1 comprises 80.5% of all meningiomas and has a benign and slow-growing histology. WHO grade 2 and 3 comprise 17.7% and 1.7% of meningioma cases respectively, and have atypical to malignant histologic features indicating a more aggressive clinical course[4]. The 10-year overall survival rates for WHO grade 1,2 and 3 tumors are 83.7%, 53%, and 0%, respectively, despite aggressive therapeutic efforts[26].

Meningiomas of any subtype with a high proliferation index have a high likelihood of recurrence and are aggressive, and are associated with WHO grade 2 and 3 meningiomas. Ki-67 proliferation indices of >4% and >20% have an increased risk of recurrence and death, respectively. Unlike glioma brain tumors, the current WHO classification system does not include any genomic or molecular features[4].

In malignancies CD44 is known to play a role in promoting tumor cell proliferation, survival, migration, invasion, and chemoresistance[13,25]. Some malignancies that have been known to be associated with CD44 are pancreatic cancer, breast cancer, prostate cancer, SCC in the head and neck and gastrointestinal cancers. CD44 may serve as a poor prognostic marker of cancer[14]. High expression of CD44 is associated with poor prognosis in WHO grade 2/3 glioma patients. In colorectal carcinoma, CD44 can be used as a biomarker of CSC, targeted therapy in patients with CD44 expression can provide better results, reduce the risk of recurrence and prevent chemotherapy resistance [27].

Several studies have found an association between CD44 expression and WHO Grade meningioma. Research conducted by Abd-Elhakeem et al. (2022) CD44 expression is associated with the grade of meningioma. Another study conducted by Mostafa & Khairy, (2017) also found that expression was higher in WHO grade 2 and 3 meningiomas (81.8%) when compared to grade 1 (18.2%). The results showed a significant association ($p<0.001$). CD44 expression can be a predictor of aggressiveness and has a tendency for progression-free survival (PFS)[16]. The results obtained in this study showed a statistically significant association between CD44 and WHO grade ($p = 0.004$).

Invasive meningiomas can be diagnosed preoperatively with conventional radiographic modalities, such as magnetic resonance imaging (MRI) and computed tomography (CT). Brain invasion in meningioma correlates with an increased risk of tumor recurrence. On multivariate analysis, the predictor factor for tumor recurrence after total resection and radiotherapy was meningioma with brain invasion. The incidence of tumor recurrence in brain-invasive tumors was increased by 2-fold[8]. Brain invasion was most common in meningiomas with WHO grade 2 and 3[28]. Invasion of the brain parenchyma occurs due to the complex involvement of adhesion molecules, extracellular matrix, basement membrane of the brain surface and growth factors. Some of the stages that occur are degradation, migration and differentiation[7].

In the invasion variable, this study found that of the 11 cases that showed weak CD44 expression, all (100%) had negative invasion. In cases with moderate CD44 expression, 15 cases (88.8%) showed negative invasion and 2 cases (11.8%) had positive invasion. In cases with strong CD44 expression, 7 cases (58.3%) had negative invasion and 5 cases (41.7%) had positive invasion. In bivariate analysis, it was found that there was a statistically significant relationship between CD44 and tumor invasion ($p = 0.023$). No study has examined the relationship between CD44 expression and tumor invasion in meningioma. In some studies it was found that high expression of membranous CD44 in high-grade meningiomas may reflect a tendency for more invasive power of neoplastic cells in surrounding tissues (dura tissue, brain, bone and other structures outside the tumor). Such findings further corroborate the theory of the role of membranous CD44 in the cellular progressivity of meningiomas[12,15,16,29].

Criteria for brain invasion should be established based on microscopic findings. There are several microscopic findings that are often misdiagnosed as brain invasion, namely: (1). Irregular protrusion into adjacent brain parenchymal tissue but there is still a leptomeningen/collagen layer between them; (2). Extension along the Virchow-Robin spaces[28]. Activation of CD44 isoforms regulates the activity of tumor invasion, migration and metastasis through several signaling pathways including enzymes, protein kinase pathways, transcription factors and intracellular pathways. In gastric cancer, the role of CD44 in invasion and metastasis is through binding with human epidermal growth factor receptor 2 (HER2) which can inhibit miR-139. Inhibition of miR-139 causes upregulation of miR-139 target gene, C-X-C chemokine receptor type 4 (CXCR4). In head and neck cancer stem cells (CSCs), the binding between CD44 and VCAM-1 can promote invasion signaling through the ezrin/PI3K pathway. Among all isoforms of CD44, CD44v shows greater affinity with HA

compared to CD44s. The binding between HA and CD44v6 can activate RTKs signaling pathways. Activation of these pathways can lead to tumor cell metastasis. In pancreatic intraepithelial neoplasia and pancreatic ductal adenocarcinoma, CD44 has an important role in upregulating the expression of EMT biomarkers namely Snail1 and Zeb1. Activation of EMT can stimulate the process of migration and invasion. In breast carcinoma, CD44 also has a very important role in regulating proliferation, invasion and migration by regulating the expression of c-Src, a key regulator in the MAPK, PI3K and STAT signaling pathways. Through activation of the Hippo-YAP oncogene signaling pathways, CD44 promotes migration and invasion of docetaxel-resistant prostate cancer cells, which have a large CD44+ population and a positive correlation with poor survival[24]. In meningiomas, CD44 is a cellular adhesion molecule associated with invasion and metastasis. Expression of CD44 signals inhibition of Merlin, a protein encoded by chromosome 22[14,30]. Merlin (moesin-ezrin-radixin-like protein) is a tumor suppressor protein. Binding between CD44 and its ligand (HA) can lead to loss of merlin expression. This can cause the tumor to progress and metastasize[31].

In some cases, heparan sulfate chains (carbohydrate side groups on the CD44 variant region) associated with regulatory growth factors activate the C-Met receptor further driving this oncogenic pathway. In addition, HA-CD44 interaction also stimulates multidrug and metabolic transporters that are strongly associated with therapy resistance. Finally, HA-CD44 interactions induce cytoskeletal changes that promote tumor cell motility and invasion[25].

The advantages of this study are that the variables and populations discussed and studied in this study are still very rarely associated, but can provide great benefits in the field of research and health in the future. The limitation of this study is the retrospective nature of the study which has limitations. Although the visual assessment was conducted by two researchers, the independence of the results from each other and the previous quantification cannot be evaluated by digital technology to corroborate the results, so it is necessary to conduct further research to assess the consistency of the results of this study. With the advent of targeted therapy, further research on CD44-targeted therapy seems important to prove the possible role of anti CD44 administration for recurrent meningioma cases. Personalized medicine will develop in the future, both for the determination of therapy, as well as patient prognosis.

5. CONCLUSIONS AND SUGGESTIONS

This study has proven that there is an association between CD44 expression with mitosis, grade and brain invasion in meningioma. Further research is needed in the form of multicenter studies to strengthen the results of this study, as well as research on therapies that target CD44 in meningioma patients.

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