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Immunohistochemical study of CD147 and matrix metalloproteases in meningiomas

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Abstract

Background/Aim: Expression of extracellular matrix proteins and metalloproteases (MMPs) has been implicated in neoplasm recurrence. Some recent studies have suggested a correlation between matrix modifier proteins and recurrence or invasion of meningiomas. Based on previous data, the aim of this study was to find a correlation between the immunohistochemical (IHC) expression patterns of a group of matrix modifier proteins, including CD147, Matrix Metalloprotease 2 and 9 (MMP2 and 9, respectively), Epithelial Cadherin (ECAD), and Galectin-3 (GAL3) with World Health Organization (WHO)-defined grade, brain invasion, recurrence, and other clinicopathological features.
Methods: This study was a cohort study. All patients with meningioma who underwent resection over a 10-year period were identified from the electronic pathology archives. Tissue microarrays (TMAs) were created for IHC studies, and IHC staining was performed using standard methodology.
Results: A total of 231 cases fulfilled the study criteria. Histological review identified 198 grade 1 tumors (85.3%), 28 grade 2 tumors (12.6%), and five grade 3 tumors (2.2%). CD147 was determined to be positively correlated with WHO-defined grade (P=0.009). ECAD, MMP2, MMP9, GAL3 were not found to be correlated with brain invasion, recurrence, or WHO grade.
Conclusion: The study results demonstrated that CD147 could be a target for diagnosis, prognosis, and treatment of meningiomas.

Keywords: meningioma, CD147, matrix metalloproteases, MMP2, MMP9, galectin-3, E-cadherin, immunohistochemistry

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Introduction

Meningiomas are the most common primary extra-axial central nervous system (CNS) tumors in adults and are thought to arise from arachnoid cells. According to the World Health Organization (WHO) 2016 criteria [1], meningiomas are classified as grades 1 through 3 corresponding to increasing recurrence risk and decreasing survival probability. WHO grade 1 meningiomas represent approximately 85% of all meningiomas and show several histological variants. WHO grade 2 represents approximately 5%–7% of all meningiomas and include the atypical, clear cell, and chordoid variants. WHO grade 3 meningiomas constitute 3% of all meningiomas and include anaplastic, papillary, and rhabdoid variants [2]. Histological grade is currently one of the most important prognostic factors. The local recurrence rate has been reported as 50%–78% for Grade 3 anaplastic meningiomas, 29%–40% for grade 2 atypical meningiomas, and 7%–20% for grade 1 meningiomas [2,3].

Extracellular matrix (ECM) proteins, metalloproteases (MMPs), and their modifier, CD147, have been implicated in many physiological and neoplastic processes, such as cell adhesion, cell migration, embryonic development, wound healing, hemostasis, oncogenic transformation, angiogenesis, and metastases and in the recurrence and invasiveness of many tumors [4]. MMPs, cadherins, especially E-cadherin (ECAD), and lectins, such as galectin-3 (GAL3) are the critical members in this group of molecules [5]. Some authors suggested that overexpression of fibronectin and GAL3 in meningiomas [6] may be associated with aggressive tumor behavior in meningiomas [7,8]. Loss of ECAD was identified in several neoplasms including meningiomas, and has been associated with tumor invasion [9,10]. In other studies, expression levels of ECAD and beta-catenin were shown to inversely correlate with invasion and recurrence of meningiomas [11]. Some studies suggested that malignant tumors express MMPs at higher levels than benign tumors although the reason and mechanism for this expression is not clear [12–15]. CD147 is a membrane glycoprotein expressed at varying levels in many cell types [16]. CD147 stimulates peritumoral fibroblasts to secrete MPPs and promotes invasiveness of various malignant tumor cells, including liver, prostate, skin, bladder, lung, and breast and was also reported in meningiomas [17]. High expression of CD147 on cancer cells was found to be positively related to cancer progression and poor prognosis [18].

The overall balance of MMPs appears to play a central role in many physiological and pathological processes. MMPs and CD147 are considered to be promising targets for cancer therapy, and so far, some synthetic and natural MMP inhibitors have been identified. However, therapeutic approaches aiming to block MMPs have not yet been successful in the treatment of cancer patients.

This study was undertaken to determine whether the matrix modifying proteins and CD147 previously associated with the behavior of meningiomas also correlate with the WHO-defined grade and hence aggressive behavior, and whether this relationship is strong enough to be relevant for clinical application.

Materials and methods

Ethics committee approval for the study was obtained from 19 Mayıs University Medical School (B.30.20DM.0.20.08/2013). This study was conducted in accordance with the Declaration of Helsinki and designed as a cohort study. Patients diagnosed with meningioma at 19 Mayıs University Medical School Hospital between 2002 and 2012 were identified based on the electronic pathology archives. The available clinical information was obtained from the electronic medical records and archived patient charts. The inclusion criteria for the study included two parameters: 1) patients with sufficient pathology material and 2) patients with the minimum necessary clinical information. Exclusion criteria were defined based on several parameters: 1) re-excision specimens, 2) patients with insufficient clinical information or pathology material, and 3) pathological diagnosis other than meningioma. All sections stained with hematoxylin and eosin (H&E) were reviewed to confirm the diagnosis of meningioma. A histological review was performed by two pathologists, and a consensus diagnosis was recorded in all cases. Each case was evaluated according to the 2016 WHO criteria and was assigned a grade and a histological type. For immunohistochemical (IHC) studies, tissue microarrays were created. IHC staining for MMP2 (PA1-16667 Thermo Fisher Scientific, 1:250), MMP9 (PA1-38182 Thermo Fisher Scientific, 1:250), ECAD (Zymed clone HECD-1; 1:100), GAL3 (Santa Cruz clone sc-32790; 1:50), epithelial membrane antigen ([EMA] Leica clone Gp1.4; undiluted), CD34 (QBEND/10, Leica; prediluted), and extracellular matrix metalloproteinase inducer (EMMPRIN)/CD147 (C-19, Santa Cruz Biotecnology, 1:50) was performed using standard methodology. CD34, EMA, and S100 protein values were used to confirm the diagnosis. The staining was interpreted in comparison with the positive controls, and the scoring was performed using a three-tiered scale: (1) 0: negative, (2) 1: focal or weak staining, and (3) 2: strong diffuse staining. Focal or weak staining implied staining of less than half of the tumor cells were at equal or lesser intensity compared to the controls. Strong diffuse staining implied positive staining of more than half of the tumor cells at equal or greater intensity compared to the controls (Figures 1–5). The presence of a correlation was investigated between these IHC staining scores and WHO grade, recurrence, and brain invasion.

Statistical analysis

In the descriptive statistics of the data, mean, standard deviation, median minimum, maximum values, frequency, and ratio values were used. To determine correlations between IHC staining and WHO grade, recurrence, and brain invasion, the chi-squared test was used in the analysis of qualitative independent data, and the Fischer test was used when the chi-squared test conditions were not met. SPSS vn.27.0 software was used in the analysis. Statistical significance was considered as $P<0.05$.

Figure 1: A: CD147 staining , score 1 (grade 1 meningioma) . B: CD147 staining, score 2 (atypical meningioma with brain invasion). C: CD147 staining, score 2 (grade3 meningioma)

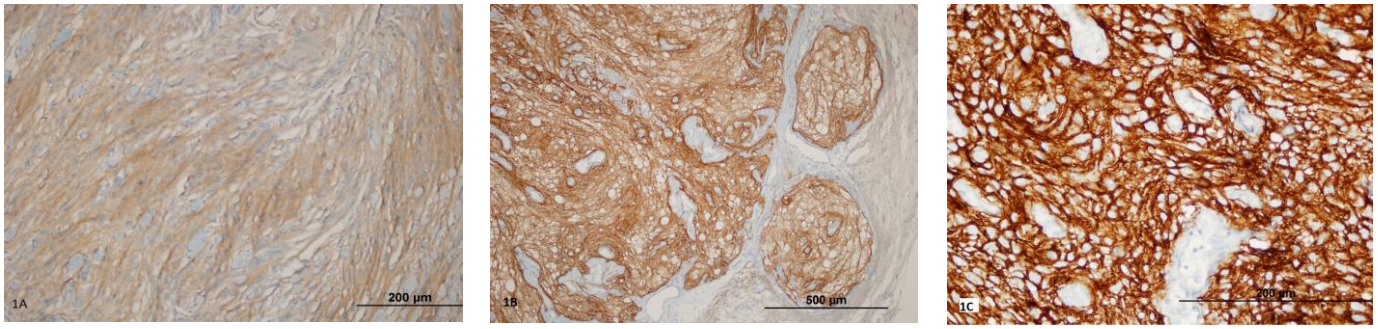


Figure 2: A: MMP2 staining, score 1, (atypical meningioma). B: MMP2 staining, score 2, (grade 1 meningioma)

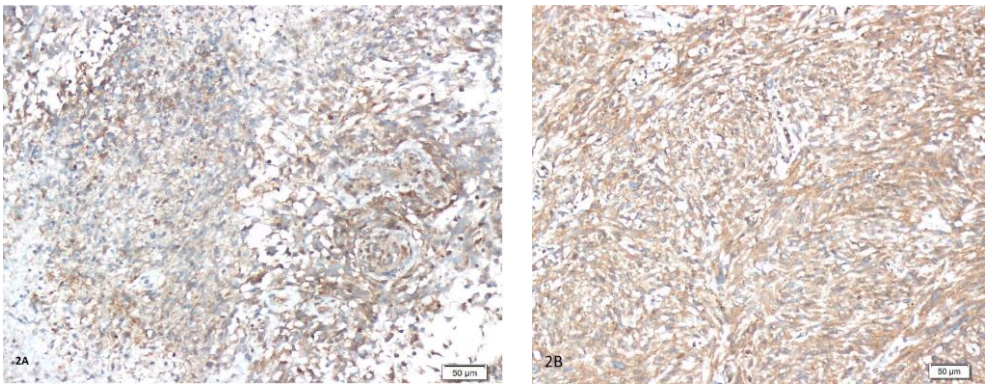


Figure 3: A: MMP9 staining, score 1, (atypical meningioma). B: MMP9 staining, score 2, (grade 1 meningioma).

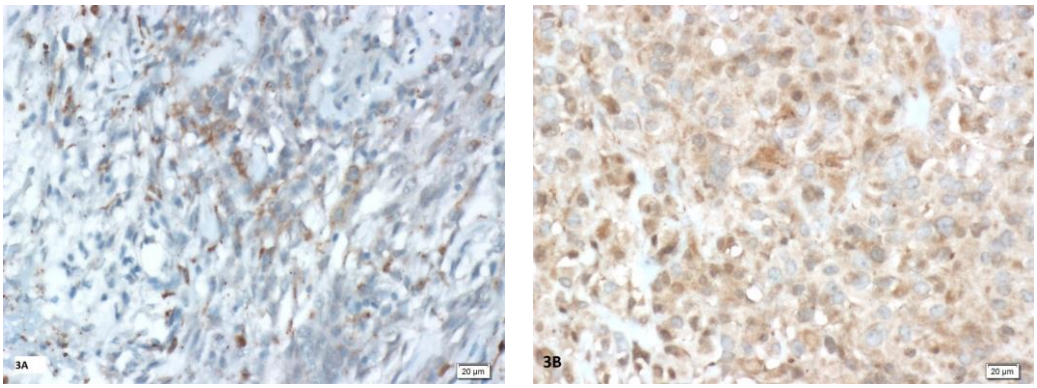


Figure 4: Galectin-3 (GAL3) staining, score 1 (anaplastic meningioma). B: GAL3 staining, score 2, (atypical meningioma).

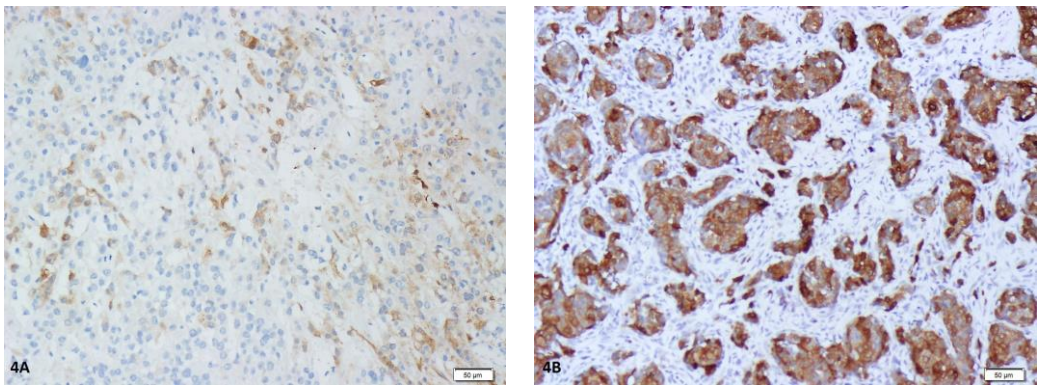
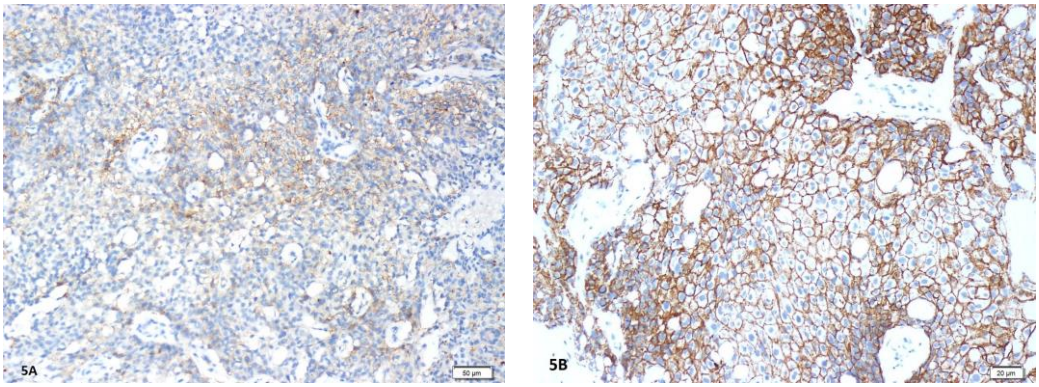


Figure 5: A: ECAD staining, score 1, anaplastic meningioma, B: ECAD staining, score 2, atypical meningioma.



Results

Of all the cases identified through the database searches, 231 cases met the study criteria. These 231 patients consisted 168 females and 63 males with a female/male ratio of 2.67. The mean and median age at diagnosis were similar at 57 years with a standard deviation of 14.4 years (range, 13–92 years). The histological review identified 198 Grade 1 tumors (85.3%), 28 Grade 2 tumors (12.6%), and five grade 3 tumors (2.2%). The distribution of the tumor grades was consistent with the previous reported series. Among the histological types, two chordoid (grade 2) and three rhabdoid (grade 3) variants were found. The majority of grade 1 tumors were of the fibrous (26%), meningothelial (25.5%), and transitional (23.4%) types. Brain parenchymal invasion was determined in 19 (8.2%) tumors. Tumors with brain parenchymal invasion were grade 2 (18 cases) or grade 3 (five cases). Recurrence information was available for 188 patients, and only 18 tumors recurred during the follow-up period (Table 1). As the number of grade 3 cases was insufficient, grades 2 and 3 were evaluated as a single group to obtain the most accurate results in the analysis of the statistical results of the IHC study. According to the results of the statistical analyses, a correlation between CD147 and WHO grade was found (P=0.009). No correlation was found between the other markers and clinical parameters (Table 2). Consistent with the literature, the rate of recurrence and brain invasion was higher in the group with grades 2 and 3 than in the grade 1 group.

Table 1: Clinical parameters of the patients included in the study.

		Min–Max	Median	Mean(SD)	%
Age (years)		13.0 - 92.0	57.0	57.0(14.4)	
TM Size (mm)		0.0 - 87.0	5.0	17.7(20.2)	
Follow Up (days)		3.0 - 3899.0	64.0	334.4(553.0)	
Gender	Female			168	72.7%
	Male			63	27.3%
WHO	Grade 1			198	85.7%
	Grade 2			28	12.1%
	Grade 3			5	2.2%
Recurrence	(-)			170	73.6%
	(+)			18	7.8%
	NA			43	18.6%
Brain invasion	(-)			212	91.8%
	(+)			19	8.2%

Table 2: Immunohistochemical scoring and statistical results

		Grade 1		Grade 2/3		*P*-value
		n	%	n	%	
CD147	No staining	54	28.3%	2	6.5%	0.009 X^2
	Weak staining	90	47.1%	15	48.4%	
	Similar or stronger staining compared to control	47	24.6%	14	45.2%	
MMP2	No staining	36	18.6%	5	15.6%	0.690 X^2
	Weak staining	86	44.3%	21	65.6%	
	Similar or stronger staining compared to control	72	37.1%	6	18.8%	
MMP9	No staining	99	50.3%	10	32.3%	0.062 X^2
	Weak staining	90	45.7%	20	64.5%	
	Similar or stronger staining compared to control	8	4.1%	1	3.2%	
Galectin	No staining	44	22.6%	7	21.9%	0.931 X^2
	Weak staining	50	25.6%	14	43.8%	
	Similar or stronger staining compared to control	101	51.8%	11	34.4%	
E-Cadherin	No staining	93	48.2%	10	32.3%	0.099 X^2
	Weak staining	70	36.3%	15	48.4%	
	Similar or stronger staining compared to control	30	15.5%	6	19.4%	

Discussion

The results of this study demonstrate that CD147 appears to be positively correlated with WHO grade in meningiomas. CD147 is a type I transmembrane glycoprotein, which belongs to the immunoglobulin superfamily and is expressed in the cell membrane in different hematopoietic, epithelial, and endothelial cell types [17,18]. Normal epithelial and fetal tissues have been shown to have low CD147 expression based on IHC analysis. However, CD147 is over-expressed in various tumors, including malignant melanoma, liver , ovarian, and lung cancers [18–20]. Recent studies have reported that CD147 plays a part in tumor proliferation, apoptosis, invasion, metastasis, multi-drug resistance, and glycolysis via the action of some molecules, such as MMPs and Caveolin [19,21]. Evidence that CD147 is overexpressed in cancers, consistent with its capability to induce MMP synthesis, suggests that this molecule acts as a key regulator of oncogenesis and is associated with one or more signaling pathways. CD147 was also identified as a poor prognostic factor in many cancers, including glioblastomas [16,20,22]. Furthermore, more recent research suggests that CD147 modulates antitumor CD8+ T-cell responses to facilitate tumor immune escape and could be a potential target for cancer immunotherapy [23].

Previous studies have suggested that MMPs have prognostic significance in meningiomas. In the current study, although no correlation was determined between MMPs and WHO grade, a strong positive correlation was determined between MMP2 and 9 expression (P<0.001), and similar strong correlations between GAL3 and MMP9 expression (P=0.001), CD147 and ECAD, MMP2 and GAL3, and between CD147 and GAL3 were found. It is possible that these molecules, which correlated with each other, are functionally interactive. Nevertheless, a direct correlation between WHO grade and matrix modifier protein expression is not easily demonstrable, and a single stain will hardly be of practical use in validating WHO grade in meningiomas. It is possible that when these molecules correlate with each other, they interact functionally.

Limited research in literature on CD147 expression in meningiomas has been published. Tsai et al. reported that “high grade brain tumors overexpressing CD147 and CD147 are positively correlated with WHO grades in human astrocytomas and meningiomas, suggesting that CD147 may be a therapeutic target in brain tumors” [22]. The current study outcome was consistent with the findings of Tsai et al. [22].

Limitations

In our study, the number of grade 3 meningiomas was low, and the clinical follow-up time was not long enough for a Kaplan–Meier survival analysis to be constructed.

Conclusion

In this study, CD147 expression based on IHC was found to be higher in high-grade meningiomas. According to the results, CD147 may be a prognostic marker and contribute to the distinguish of Grades 1 and 2 meningiomas, especially in cases with diagnostic difficulties, and more importantly, it may be a target for meningioma treatment. The need for further studies to support these findings exists.

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