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RESEARCH STUDY

DIFFERENCES OF VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) EXPRESSION IN VARIOUS MENINGIOMA EDEMA INDEX

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ABSTRAK

Latar Belakang: Meningioma adalah tumor intrakranial utama paling umum pada dewasa setelah glioma. Vascular endothelial growth factor (VEGF) adalah protein kunci dalam pembentukan pembuluh darah baru (angiogenesis). Pada meningioma, pengikatan VEGF ke VEGF reseptor (VEGFR) melalui aktivasi penyinalan Ras/MAPK *pathway* serta pengontrolan permeabilitas vaskuler melalui PLCγ *pathway* berperan utama dalam pembentukan pembuluh darah baru bersifat imatur yang sangat permeabel sehingga dapat menyebabkan kebocoran protein plasma di dalam tumor yang mencetuskan edema peritumoral (PTBE). Enam puluh persen meningioma terkait dengan kejadian *peritumoral brain edema* (PTBE).
Tujuan: Penelitian ini bertujuan untuk mengetahui perbedaan ekspresi VEGF pada berbagai indeks edema meningioma.
Metode: Penelitian observasional analitik dengan *consecutive sampling* pada 69 sampel yang didiagnosis meningioma dengan data MRI. Variabel ekspresi VEGF berdasarkan Immunohistokimia digolongkan menjadi skor 0, 1+ dan 2+. Variabel PTBE Meningioma dinilai dengan Indeks edema berdasarkan MRI digolongkan menjadi derajat 1,2 dan 3.
Hasil : Berdasarkan uji korelasi Spearman, tidak terdapat perbedaan yang signifikan antara ekspresi VEGF pada berbagai indeks edema meningioma (p = 0,333).
Kesimpulan: Tidak terdapat perbedaan yang signifikan antara ekspresi VEGF pada berbagai indeks edema meningioma (p = 0,333).
Kata Kunci: Meningioma, edema peritumoral, angiogenesis, *vascular endothelial growth factor*

ABSTRACT

Background: Meningiomas are the most common primary intracranial tumor in adults after glioma. Vascular endothelial growth factor (VEGF) is a key protein in the formation of new blood vessels (angiogenesis). In meningiomas, binding of VEGF to the VEGF receptor (VEGFR) through activation of the Ras/MAPK signaling pathway and control of vascular permeability through the PLCγ pathway peritumoral (PTBE). Sixty percent of meningiomas are associated with peritumoral brain edema (PTBE).
Objective: This study aims to determine differences in VEGF expression on various indices of meningioma edema.
Methods: An analytical observational study with consecutive sampling in 69 samples diagnosed with meningioma with MRI data. VEGF expression variables based on Immunohistochemistry were classified into scores of 0, 1+ and 2+. Variable PTBE Meningiomas assessed by the edema index based on MRI were classified into grades 1,2 and 3.
Results: Based on Spearman's correlation test, there was no significant difference between VEGF expression on various meningioma edema indices ($p = 0.333$).
Conclusion: There was no significant difference between VEGF expression on various meningioma edema indices ($p = 0.333$).

Keywords: Meningioma, peritumoral edema, angiogenesis, vascular endothelial growth factor

INTRODUCTION

Meningiomas are the most common primary intracranial tumor in adults after glioma. Based on data from the Central Brain Tumor Register of the United State, the annual incidence of meningiomas is 8.33 per 100,000 population.[26]

Several factors of biomarker related to the molecular biology of meningiomas have been studied, one such biomarker is vascular endothelial growth factor (VEGF), a major inducer of physiological and pathological angiogenesis.[59] In meningiomas, the binding of VEGF to the VEGF receptor (VEGFR) through the activation of the Ras/MAPK signaling pathway and the control of vascular permeability through the PLCγ pathway play a major role in the formation of new, highly permeable immature blood vessels that can cause leakage of plasma proteins within the tumor, triggering peritumoral edema. (PTBE). Sixty percent of meningiomas are associated with peritumoral brain edema (PTBE).[2] PTBE was defined as a high-intensity signal observed around the brain tumor on T2-weighted MRI.[11] The relationship between tumor and PTBE volume can be determined by the Edema index using the formula ((VT2-high-Vtumor) / Vtumor).[10] PTBE in meningiomas can be aggravating clinical symptoms, positively correlated with seizures, postoperative side effects and high recurrence rates.[5,10]

MATERIALS AND METHODS

This study was performed after obtaining ethical clearance from the Ethical Clearance Committee from the Health Research Ethics Commission (KEPK) RSUP Dr.Kariadi, with the reference number No.992/EC/KEPK-RSDK/2021 and research permit with the reference number DP.02.01/I.II/9267/2021. The study applied a retrospective, descriptive analytic, cross-sectional design by performing immunohistochemistry examinations of paraffin blocks meningioma tissue samples with MRI data.

The study was performed in the Anatomical Pathology Laboratory, RSUP Dr.Kariadi, Semarang from May 2021 to August 2021. The study population consisted of HE (Hematoxylin and Eosin) slides and paraffin blocks diagnosed with meningiomas of all degrees with MRI data from January 1st, 2018 to December 31st, 2021.

Sixtynine samples were obtained. Paraffin blocks were collected at the Anatomical Pathology Laboratory, RSUP Dr.Kariadi, Semarang and MRI data, whereas patients' MRI were collected at Radiology unit, RSUP Dr. Kariadi.

Sampling was done by consecutive sampling, where the researcher includes all samples that meet the inclusion criteria until the number of samples required was fulfilled.

In the paraffin block, immunohistochemical examination was performed to determine the expression VEGF. Immunohistochemical examination is an examination of tissue that has been labeled with specific antibodies to see the expression of specific antigen proteins under a microscope.

Edema index from MRI data was read by Radiologist. The tools needed for this research were: microtome water bath, hot plate, freezer, incubator,staining jar, object glass rack, micro pipette, filter paper, 15 ml centrifuge tube, entelan and light microscope and Microdicom software.

VEGF expression and Edema Index in cases of meningiomas were assessed.

The expression of VEGF which was painted positive was brown in the cytoplasm of tumor cells and the cytoplasm of tumor blood vessel endothelial cells, were, in average rating in 10 fields of view with 200x magnification, with score category:

- score 0 if there are no or few cells (less than 10% of stained cells),
- score 1+ if stained moderately or rarely intensively (10-50% of stained cells)
- score 2+ if strongly diffusely stained (more than 50% of stained cells).[2,10]

Results by agreement between readers when the result is more than 0.5, rounded to the score above it.

The relationship between peritumoral brain edema (PTBE) volume and meningioma tumor volume was defined as Edema index (EI). Evaluation of PTBE volume measurements on T2-weighted or fluid-attenuated inversion recovery scans of tumor volume using MRI were each measured by the formula (V=4 abc/3), whose relationship between the two was defined as Edema index (EI) using EI formula = (VT2-high – Vtumor)/Vtumor, with grade category:

- grade 0, no edema or negligible edema (EI<0.1)
- Grade 1, mild edema (0.1<EI<1.0)

- Grade 2, moderate edema (1.0<EI<2.0)
- Grade 3, severe edema (EI>2).[10]

STATISTICAL ANALYSIS

All data obtained were analyzed statistically using the statistical package for social sciences (SPSS) program, version 15 (SPSS Inc). Comparative analysis was performed to assess significance with $p < 0.05$.

RESULT

69 paraffin blocks were obtained from meningioma patients with MRI data who underwent surgery at Dr. Hospital. Kariadi Semarang who met the research criteria. This amount corresponds to the minimum number of samples based on the sample size formula. From the previous 70 study samples, 1 sample was excluded because meningiomas with vasogenic edema were not due to tumors. Subjects included in the research inclusion criteria are shown in table 1:

Table 1 Subjects fit the research inclusion criteria

No sample	Age/gender	Location	Type of histology	Grade	Volume tumor cm^3	VEGF	PTBE
1	49/P	Frontobasal	Microcystic	I	4,09	1+	1
2	49/P	Tentorium	Atypical	II	22,7	1+	0
3	39/P	Clivus	Atypical	II	13,5	0	0
4	42/P	Tuberculum sella	Transitional	I	6,69	1+	1
5	52/P	Tuberculum sella	Fibrous	I	3,29	0	0
6	43/P	Frontobasal	Angiomatous	I	6,29	1+	3
7	54/P	Sphenoid ridge	Fibrous	I	3	0	0
8	46/P	Konveksitas	Fibrous	I	21	1+	0
9	45/P	Sphenoid ridge	Meningothelial	I	4,22	0	0
10	50/P	Frontobasal	Transitional	I	11,2	1+	2
11	44/P	Falx	Transisional	I	6,56	2+	0
12	53/P	Fossa media	Meningotelial	I	3,3	0	3
13	43/P	Sphenoid ridge	Meningotelial	I	9,8	0	3
14	32/P	Parasagital	Meningotelial	I	7,16	1+	3
15	48/P	Tuberculum sella	Meningotelial	I	8,13	1+	3
16	46/P	Sphenoid ridge	Meningotelial	I	0,64	1+	0
17	59/P	Tuberculum sella	Fibrous	I	7,09	2+	0
18	40/P	Tuberculum sella	Transisional	I	53,72	0	0
19	57/P	Sphenoid ridge	Transisional	I	17,53	0	2
20	59/L	Falx	Atypical	II	38,4	2+	2
21	40/P	Tuberculum sella	Fibrous	I	0,83	0	0
22	66/P	CPA	Transitional	I	8,39	1+	1
23	30/P	Frontobasal	Transisional	I	21,06	1+	0
24	55/P	Sphenoid ridge	Fibrous	I	22,5	1+	0
25	53/P	Falx	Meningothelial	I	3	1+	3
26	49/P	Sphenoid ridge	Meningothelial	I	12,23	0	1
27	47/P	Sphenoid ridge	Transisional	I	31,3	1+	0
28	42/P	Tuberculum sella	Transisional	I	11,2	1+	0
29	50/P	Parasagital	Fibrous	I	25,4	1+	1
30	53/P	CPA	Meningothelial	I	11,24	1+	0
31	45/P	Fossa media	Transisional	I	26	1+	1
32	37/L	Falx	Meningoteliall	I	25,53	1+	2
33	55/P	Sphenoid ridge	Meningothelial	I	2,13	1+	0
34	44/P	CPA	Meningothelial	I	9,02	0	0
35	35/P	Tuberculum sella	Meningothelial	I	3,46	1+	0
36	54/P	Tuberculum sella	Angiomatous	I	3,07	0	0
37	56/P	Tentorium	Transisional	I	3,39	2+	2
38	44/P	Tentorium	Chordoid	II	0,77	1+	3
39	51/P	Falx	Fibrous	I	4,377	0	0
40	47/P	Tuberculum sella	Tidak dpt ditentukan karena sel sedikit	I	4,93	1+	0
41	49/P	Konveksitas	Tidak dpt ditentukan	I	13,29	1+	0
42	41/P	Sphenoid ridge	Transisional	I	18,93	2+	1

43	45/P	Tuberculum sella	Meningotelial	I	1,51	1+	3
44	45/P	Sphenoid ridge	Meningotelial	I	2,94	1+	0
45	50/P	Sphenoid ridge	Microcystic	I	1,88	1+	0
46	51/P	Parasagital	Angiomatous	I	6,94	1+	3
47	56/P	Sphenoid ridge	Meningotelial	I	1,74	1+	0
48	66/P	Parasagital	Meningothelial	I	8,04	1+	3
49	46/P	Fossa media	Microcystic	I	27,8	1+	1
50	43/P	Konveksitas	Transitional	I	2,03	2+	0
51	48/P	Tuberculum sella	Meningotelial	I	3,588	0	0
52	55/L	Parasagital	Transisional	I	14,7	1+	2
53	56/P	Falx	Atypical	II	29,7	1+	1
54	43/P	CPA	Meningotelial	I	13,1	0	0
55	40/L	Konveksitas	Transisional	I	3,63	1+	0
56	43/P	Clivus	Psammomatous	I	3,25	1+	0
57	47/P	Frontobasal	Transisional	I	23,76	1+	1
58	48/P	Clivus	Transisional	I	9,87	1+	1
59	61/P	CPA	Transisional	I	3,17	1+	0
60	57/P	Tuberculum sella	Transisional	I	6,65	1+	0
61	53/P	Frontobasal	Transisional	I	48,6	1+	0
62	50/P	Fossa media	Microcystic	I	18,27	0	2
63	43/P	Clivus	Microcystic	I	1,25	1+	0
64	51/P	CPA	Transisional	I	0,75	0	0
65	39/P	Konveksitas	Microcystic	I	34,7	1+	0
66	52/P	Sphenoid ridge	Meningotelial	I	10,47	0	0
67	50/P	Frontobasal	Fibrous	I	20,71	0	1
68	40/P	Parasagital	Meningotelial	I	19,75	1+	0
69	44/P	Frontobasal	Meningotelial	I	12,69	1+	1

Table 2 Clinical, histopathological, radiological characteristics of research subjects

Variabel	F	%	Mean ± SD	Median (min – max)
Age			48,04 ± 7,16	48 (30 – 66)
Gender				
Male	4	5,8		
Female	65	94		
Location				
Tuberculum sella	13	18,8		
Sphenoid ridge	13	18,8		
Frontobasal	8	11,6		
Konveksitas	7	10,1		
Parasagital	6	8,7		
Falx	5	7,2		
Fossa media	5	7,2		
CPA	5	7,2		
Clivus	4	5,8		
Tentorium	3	4,3		

Histology type				
Transisional	21	30,4		
Meningotelial	22	31,9		
Fibrous	9	13,0		
Microcystic	6	8,7		
Atypical	4	5,8		
Angiomatous	3	4,3		
Chordoid	1	1,4		
Psammomatous	1	1,4		
Tak dapat ditentukan	2	2,9		
Histology grade				
I	64	92,8		
II	5	7,2		
Meningioma size			12,20 ± 11,58	8,13 (0,64 – 53,72)
PTBE				
0	39	56,5		
1	13	18,8		
2	7	10,1		
3	10	14,5		
VEGF				
0	19	27,5		
1+	44	63,8		
2+	6	8,7		

VEGF expression and Peritumoral brain edema index

VEGF expression was assessed in meningioma and vascular endothelial cells of meningioma (Fig. 12), scored 0 if there were no or few stained cells in the cytoplasm (less than 10% of stained cells), 1+ if moderately or intensively stained diffusely (10-50% stained cells), 2+ if strongly diffusely stained (more than 50% stained cells).[2] (Figure 1) The results of VEGF expression are listed in table 2 above.

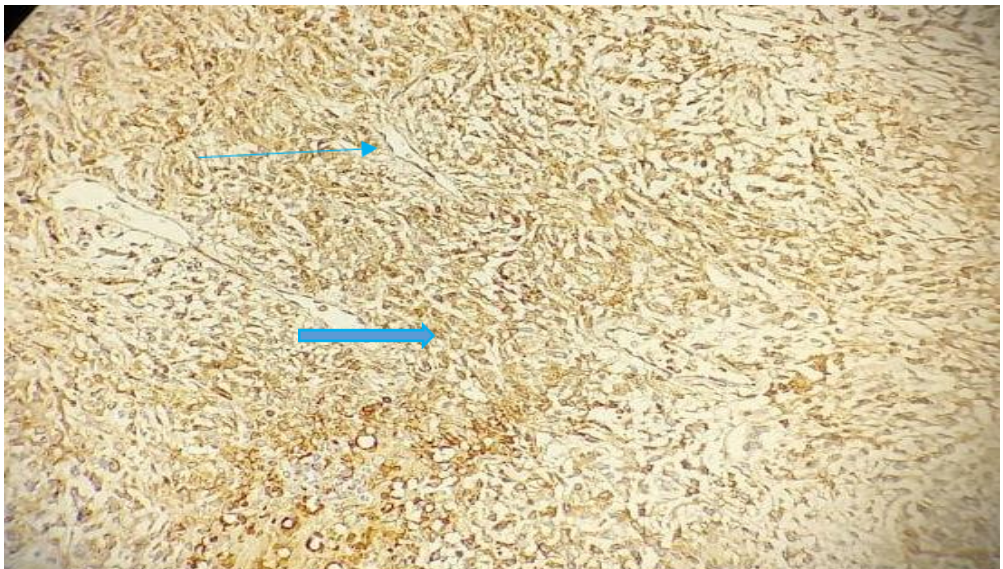

Figure 1. VEGF expression in meningioma cells (→) and meningioma blood vessel endothelium (⟶) (immunohistochemistry, 200x magnification).

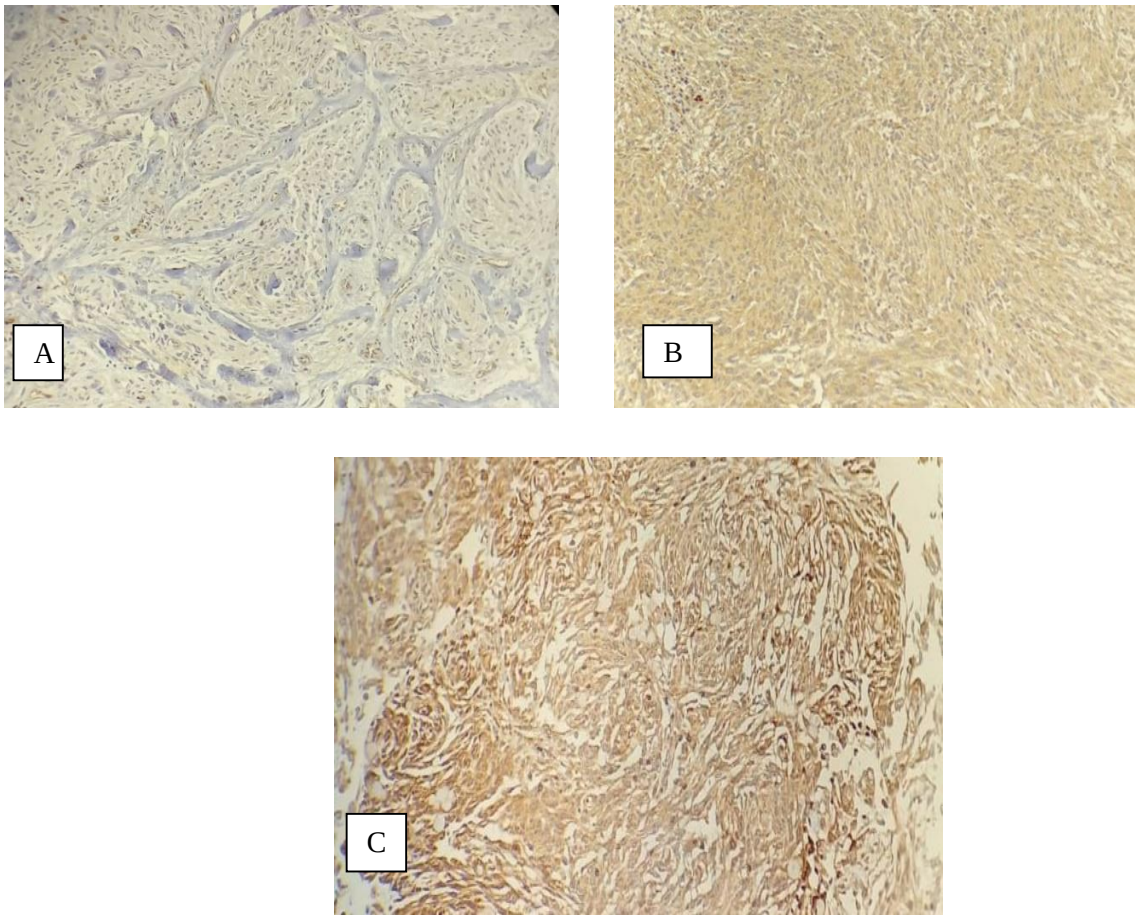

Figure 2. Expression of VEGF in meningioma cells and meningioma vascular endothelium (immunohistochemistry, 200x magnification). A. score 0 if there are no or few stained cells in the cytoplasm (less than 10% of stained cells). B. Score 1+ if stained moderately or intensively rarely (10-50% of stained cells). C Score 2+ if strongly diffusely stained (more than 50% of stained cells)[2]

In this study, formula's Peritumoral brain edema index was graded as grade 0 when there was no edema or negligible edema (EI<0.1); grade 1, mild edema (0.1<EI<1.0); grade 2, moderate edema (1.0<EI<2.0); grade 3, severe edema (EI>2).[10] In this study, 56% PTBE 0, 18.8% PTBE grade 1, 10.1% grade 2, 14.5% grade 3.

Differences in VEGF expression in peritumoral edema meningioma

From the results of the Spearman's correlation test between VEGF and PTBE, the p value = 0.333 and r = 0.118, because the p value > 0.05, it can be concluded that there is no significant difference between VEGF and PTBE.(table 5)

Table 3. Table of differences between VEGF and PTBE (Spearman's correlation test)

VEGF	PTBE				p	r
	0	1	2	3		
0	13	2	2	2	0,333	0,118
1+	23	10	3	8		
2+	3	1	2	0		

DISCUSSION

Based on gender, this study obtained 69 samples, 94.2% female (65/69) and 5.7% male (64/69). This data is in accordance with global data, the International Agency for Research on Cancer (IARC) which also states that the incidence of meningioma in women is higher than men.[1] This is also in accordance with several previous studies, where a retrospective study in 2019 reported that the female sex was 73% (44/60) and the male was 27% (16/60).[32] Based on CBTRUS data, in 2011-2015, it was also found that women are more often affected by meningiomas than men.[22] The difference between women and men is mentioned because in the growth of Meningiomas, there is an important role of estrogen and progesterone which are the dominant hormones in women.[12,19] Various studies show that most meningiomas express progesterone hormone receptors on cell membranes, with various variations.[56,61]

Based on age, in this study it was found range age patient between 32 years old up to 66 years , with average 48 years old . The results of this study showed that the most meningioma patients were in the fifth decade of 40-49 years, namely 34 people (49.2%), followed by the age range 50-59 years as many as 26 people (37.68%), the age range 30-39 years as many as 6 people (16.8%) and 3 people (4.3%) , with an average age of 48 years . Results study with range age highest on 40-49 years old this also reported on study retrospective in 2021 and 2017. [56.57] A similar mean age was also

reported in a 2013 retrospective study indicating the mean age was 44.7 years (range from 24-65 years). [42] Average age on this study more young compared to data from CBTRUS 2005-2009 which is 66 years. [1] The reason for this shift in the younger mean age is not yet known, however deletion and inactivation of the neurofibromatosis 2 (NF2) gene locus, which is a tumor suppressor gene, is believed to be a predominant factor in the incidence of sporadic meningiomas.[56]

Based on the type of histopathology, in this study , the most dominant type was Meningothelial (31.8%), slightly different from Transitional (30.4%). Other histology type is Fibrous (13%), Microcystic (8.6%), Atypical (5.7%), Angiomatous (4.3%), Chordoid (1.4%), Psammomatous (1.4%), and 2.8% could not determined because due to the small number of cells. In line with retrospective study in 2014 and 2020 , the most common type is the Meningothelial type .[58.59] However, it is different from the results of a retrospective study in 2014 where the most common type is transitional (47.8%) followed by meningothelial (19.6%).[42] The same thing was also obtained in the 2021 study where the transitional type was the most (41.1%) followed by angiomatous (4.7%).[56] Also in a retrospective study in 2021, transitional was found to be the most common meningioma subtype (43%), followed by fibroblastic (22%) and meningothelial (15%).[62] It is stated in the literature that there is an influence of the expression of the hormone progesterone receptor on the meningioma cell membrane, which is highest in the transitional meningioma type and the well-differentiated transitional meningioma tissue has many similarities with normal arachnoid cells, resulting in Transitional Meningioma having the highest subtype in Meningioma.[56] However, this information differs from the 2021 retrospective study in which meningothelial and psammomatous tumors showed slightly higher levels of PR expression (76 and 77%, respectively) than transitional (63%) and fibroblastic (52%), but without statistical significance. [62]

Based on the histological grade, in this study, the majority of meningiomas were low grade (grade I) which was 92.7% (64/69), and high grade (grade II) was 7.2% (5/69). This is in accordance with the previous retrospective study in 2014 where the most cases obtained were low grade (grade I) 68% (93/136) while high grade (grade II and III) was 31.6% (43/136) and data from retrospective studies in 2018 obtained 81% grade I and 19% grade II.[2,60] Data from WHO 2016 also states that low-grade meningiomas (grade I) are the most common meningiomas compared to meningiomas grades II and III, which

are 20-25% and 1-6% in grades II and III, respectively.[1] It is said that there is a relationship between Progesterone expression and tumor grade where the PR expression score in grade I meningiomas is higher than grade II and III, where progesterone is normally expressed in small amounts of non-neoplastic meningothelial cells, which then increases when cell proliferation occurs, as in meningiomas, and decreases when there is a change in cell differentiation as in the increasing grade of meningiomas. The role of progesterone receptors also affects the incidence of meningiomas more in women than men. [62]

Based on tumor size, this study obtained a size range between 0.6 cm^3 to 53.7 cm^3, with an average size of 12.2 cm^3. The average meningioma size in this study is approximately the same as the average meningioma size in a retrospective study in 2011, which obtained an average of 8.81 cm^3 in meningiomas without edema and 36.28 cm^3 in meningiomas with edema.[11]

Based on location, in this study, the tubercle sella and sphenoid ridge were the most common locations (18.8%), followed by frontobasal (11.5%), convexity (10.1%), parasagittal (8.6%) , falx, middle fossa and CPA (7.2%), clivus (5.7%) and tentorium (4.3%). This is different from the previous retrospective study in 2008 where the highest location was found in convexity and the previous retrospective study in 2013 also found the most location was convexity.[10,43] This difference could be due to the fact that only samples with MRI data were selected, so it may not be possible to select representative of the entire meningioma sample.

Expression VEGF

In this study, there were 50 cases of Meningiomas with positive VEGF expression in tumor cells and endothelial cells of 72.4% (50/69) with 63.7% (44/69) showing a score of 1+ and 8.6% (6/69) showing a score of 2+. This is consistent with the previous retrospective study in 2002, which found a positive VEGF expression of 84.3% (27/32) and a retrospective study in 2013 of 69.6% (32/46).[14,42] This difference in expression may be due to differences in immunohistochemical staining procedures, differences in reading methods and cut-off values, types of antibodies used and differences in the number of samples. In this study using a score of 0 if there are no stained cells or few stained cells (less than 10% stained), 1+ if tumor or endothelial cells stained moderately or intensively rarely (10-50% stained cells), 2+ if strongly

diffusely stained (more than 50% of cells stained), similar to the retrospective study in 2014.[2] In a retrospective study in 2002 with a difference using a positive assessment if the positive cells were more than and equal to 5% of stained cells and a retrospective study in 2013 with an assessment of the intensity and percentage of stained cells where a score of 1 if the intensity was weak in less than 10% of tumor cells only or stained tumor cells and endothelial cells and a score of 2 if the intensity is weak to moderate in 10-50% of tumor cells only or tumor cells and stained endothelial cells.[2,14,42] The antibodies used in this study were mouse monoclonal VEGF antibody (C). -1): sc-7269 produced by Santa Cruz, whereas in a retrospective study in 2013 using monoclonal antibody Ventana and a retrospective study in 2013 using rabbit polyclonal antibody VEGF 165 isoform, Biogenex.[2,14]

Peritumoral brain edema (PTBE)

In this study PTBE was found in 43.4% (30/69) cases of meningioma with 18.8% (13/69) PTBE grade 1, 10.1% (7/69) grade II and 14.4% (10/29). 69) III degree. This is consistent with a previous retrospective study in 2011 which found 42.5% (43/101) of cases with PTBE and a retrospective study in 2014 found 67.6% of cases with PTBE (92/136).[2,12]

Expression VEGF with PTBE Meningioma

In a retrospective study in 2002, it was found that all meningiomas expressing VEGF were not strongly associated with PTBE, especially in groups with the same degree of PTBE, the results of the Western blot of VEGF varied, although Immunohistochemical staining showed some correlation with PTBE severity (p=0.315).[9] Even some meningiomas with high VEGF do not show PTBE, while some with low VEGF values show extensive PTBE.[9]

A retrospective study in 2021 found that there was no significant relationship between VEGF-A and VEGF R1 meningiomas (p=0.1) and no significant relationship was found between VEGF and PTBE in meningiomas.[52] Similar things happened in this study, where there was no significant difference between VEGF expression on various edema index Meningioma (p = 0.333).[19]

From the data obtained in this study where 2 study samples with a VEGF

score of 0 with PTBE grade 3 can provide evidence that peritumoral edemagenesis is a multifactorial process in which VEGF plays an important role but does not play a significant role in the process of peritumoral edemagenesis.[16] Likewise, from the three samples obtained with a VEGF 2+ score with PTBE grade 0, it shows that there are factors that do not support the process of edemagenesis. [16]

Hypoxic conditions are strong stimulators of VEGF secretion. HIF-1 binds to VEGF in helping cells cope with decreased oxygen conditions. In a retrospective study in 2002, there was a strong relationship between HIF-1 and VEGF (p=<0.0004).[28] The retrospective study in 2020 found a significant relationship between HIF-1α and PTBE meningiomas (p=0.023).[53] However, it is possible that the tumor grows slowly enough that it never enlarges and exceeds its blood supply so that there is no hypoxic state that triggers HIF-1 which binds to VEGF thereby triggering edema. This is supported by the results of a retrospective study in 2011 that there is no relationship between tumor size and PTBE (p=0.537).[11] In this condition, there are other factors that play a role in triggering the hypoxic meningioma condition that triggers VEGF other than meningioma size.

In the hydrodynamic theory related to the pathogenesis of PTBE, there is the concept of intra-tumoral congestion in which a 2006 retrospective study found a significant relationship between PTBE and tumor efferent vein hypoplasia using superselective angiography where efferent venous hypoplasia of meningiomas was associated with a significantly higher edema index (Fig. p<0.001)[26]. Taken together these angiographic findings suggest that if the tumor or part of the tumor has a good drainage system, then no edema is formed, whereas if the tumor does not have a drainage system, then significant PTBE will develop.[26]

In addition to the condition of efferent venous hypoplasia, a 2014 retrospective study also showed that there was a significant relationship between VEGF expression and blush on meningioma angiography (p=0.0005) and a significant relationship between VEGF expression and meningioma edema index (p=0, 0001).[14] In that study, the edema index was significantly associated with pial blood in meningiomas.

Besides of the above factors , angiogenesis depends on a balance between angiogenic and antiangiogenic agents. Recently this has proven that activity VEGF

proangiogenics can opposed by factor antiangiogenic semaphorin 3A (SEMA3A). SEMA3A is a guide protein owned axon by class 3 semaphorins (SEMA) that exert the action through binding to neuropilin-1 (NRP-1), a protein identified on cell nerves , and also expressed on cell endothelium as transmembrane receptors that direct on apoptosis and inhibition proliferation endothelial cells .[26] However, NRP-1 also functions as an adjunct receptor for VEGF and mediates its activity in the absence of the VEGF-R receptor. In addition, NRP-1 can also enhance the binding effect of VEGF to VEGFR-2. Thus, SEMA3A acts as an antiangiogenic factor either directly, by binding to NRP-1, or indirectly, by competitive inhibition of NRP-1 binding to VEGF. SEMA3A expression was recently demonstrated in human meningioma neoplastic cells, and it has been suggested to behave as an anti-angiogenic factor in these tumors via NRP-1 binding. Therefore, neoangiogenesis in meningiomas may be regulated by the balance in VEGF and SEMA3A concentrations in the tumor microenvironment rather than by VEGF alone. Thus, neoangiogenesis will be blocked or stimulated depending on the prevalence of VEGF or SEMA3A. [25] This is supported by the results of a retrospective study in 2019 that the tumor edema index was negatively related to tissue semaphorin expression in this case semaphorin 3C ($p=0.048$).[54]

VEGF expression can be reduced with dexamethasone.[25] Dexamethasone is still the therapy of choice in reducing preoperative edema, including in the hospital where the researchers studied. However, a retrospective study in 1994 found no significant reduction in the area of edema and tumor area of meningioma with dexamethasone administration.[47] This is supported by the persistence of intraoperative meningioma edema in the research hospital after preoperative administration of dexamethasone. To date, limited data have been published describing the antiedemagenic and antitumor activity of VEGF-directed therapy in meningiomas.[3] A retrospective study in 2022 showed statistical differences in progression free survival (PFS) and overall survivorship (OS) between groups treated Bevacizumab-treated versus non-Bevacizumab-treated at 12 and 36 months after surgery ($P<0.05$). However, there was no significant difference in PFS and OS in the two groups at 60 months postoperatively ($P > 0.05$).[49] This suggests that VEGF activation is not the main driver of angiogenesis in meningiomas, in line with the results of a retrospective study in 2012.[48] Several studies with poor anti-VEGF

response to Meningioma edema, suggest that anti-VEGF therapy is only beneficial under certain conditions, such as the presence of a cerebral blood supply and a high ratio of VEGF to semaphorine 3 A. Further evaluation of this issue is still needed to determine determine which types of patients will respond well to anti-VEGF therapy. Based on this study, it was found that there was no significant difference between VEGF and PTBE Meningiomas, therefore we do not recommend the use of VEGF as a routine examination in meningiomas.

CONCLUSION

The results of this study state that there is no significant difference among VEGF expression in various meningioma edema index ($p = 0.333$). [19] Based on the results of the research and discussion carried out, it can be concluded as of the following: VEGF expression was positive in 50 of 69 cases of meningioma (72.4%), consisting of of 63.8% score 1+ and 8.7% score 2+ . Meningioma PTBE were obtained as follows: 30 of 69 cases with PTBE (43.4%), consisting of from 18.8% with edema index grade 1; 10.1% grade 2 and 14.5% grade 3 . Meningioma histological type were obtained as follows: Meningothelial (31.8 %), Transitional (30.4%), Fibrous (13%), Microcystic (8.6%), Atypical (5.7%), Angiomatous (4.3%), Chordoid (1.4%), Psammomatous (1.4%), and 2.8% could not be determined due to the small number of cells. Meningioma histological grades were obtained as follows: Low grade meningioma (grade I) was 92.7% (64/69), and high grade (grade II) was 7.2% (5/69). Meningioma location were obtained as follows: tubercle sella (18.8%), sphenoid ridge (18.8%), followed by frontobasal (11.5%), convexity (10.1%), parasagittal (8.6%), falx , middle fossa and CPA (7.2%), clivus (5.7%) and tentorium (4.3%). Meningioma tumor size were obtained range between 0.6 cm^3 up to 53.7 cm^3 , with an average size of 12.2 cm^3. There was no significant difference between VEGF expression in various meningioma edema indices ($p = 0.333$).

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