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The Association of Fibulin-2 Expression with Histopathological Grade and Fibrotic Tumor Vessel in Meningioma

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ABSTRACT

Background
Meningiomas are the most common primary tumors of the central nervous system. About one-fifth of meningiomas tend to recur. The World Health Organization (WHO) histopathological grade was the most useful morphological predictor of recurrence. Fibrotic tumor vessels (FTV) were detected in nearly half of WHO grade I meningiomas and correlated with vascular density and increased risk of recurrence. Fibulin-2 is an extracellular matrix glycoprotein whose expression increases in traumatic central nervous system injuries and can be used as a marker to differentiate the histopathological grade of meningiomas. This study aimed to determine the association of fibulin-2 expression with histopathological grade and FTV in meningiomas.

Methods
This research was an observational cross-sectional study. The study sample was 36 cases of meningioma in three Anatomical Pathology laboratories in West Sumatra on period January 2019 to December 2020. Samples obtained from resected meningioma cases were then reevaluated on Hematoxylin Eosin (HE) slides to determine the histopathological grade and FTV. Van-Gieson staining was performed to confirm FTV. Fibulin-2 expression in tumor cells was analyzed using immunohistochemical staining. Bivariate statistical analysis using the Chi-Square test with $p<0.05$ was considered significant.

Result
High-risk meningiomas (WHO grade II and III) showed high fibulin-2 expression (62.5%), whereas low-risk meningiomas (WHO grade I) were more abundant with low fibulin-2 expression (75%). The presence of FTV at low fibulin-2 expression was 58.3%. Statistical analysis showed no significant association between fibulin-2 expression with histopathological grade ($p=0.077$) and FTV ($p=1,000$).

Conclusion
In summary, the study showed that fibulin-2 expression was not associated to histopathological grade nor to FTV in meningiomas.

Keywords: meningioma, fibulin-2 expression, histopathological grade, fibrotic tumor vessel.

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INTRODUCTION

Meningioma is the most common primary tumors of the central nervous system, accounting for more than 25,000 meningiomas diagnosed in the United States each year.[1] Based on data from the Central Brain Tumor Registry of the United States (CBTRUS) released in 2021, it was found that the incidence of meningiomas was 39% of all brain tumors and 54.5% of all benign brain tumors in 2014-2018.[2] In Indonesia, data from GLOBOCAN 2020 shows brain tumors (central nervous system) rank 15th with 5964 new cases (1.5%).[3] Studies in five Anatomical Pathology laboratories in West Sumatra found 85 cases of meningioma from 2012-2015.[4]

Complete tumor resection is the main therapeutic option for meningioma, but 20% of meningiomas will recur after initial surgical operation.[5.6] Each recurrence of the meningioma carries a further risk of recurrent surgery and a much greater risk of morbidity and mortality for the patient.[7] Benign meningiomas have the recurrence rates of about 7-25%, whereas atypical meningiomas recur in 29-52% of cases and anaplastic meningiomas at rates of 50-94%.[8] Recurrence rates in some cases of meningiomas are also associated with tumor vascularization patterns and peritumoral brain edema rates.[9]

Meningiomas are highly vascular tumors and may require neovascularization for enlargement.[10] In the histological classification, not only the number/density of blood vessels but also the composition of blood vessels seems to be important. Research conducted Hess et al (2020) in grade I meningioma showed a correlation between vascular density and fibrosis in tumor blood vessels with the prognosis of meningiomas. Fibrotic tumor vessels (FTV) were detected in 48% of grade I meningiomas and correlated with vascular density. The occurrence of FTV correlates with a two-fold increase in the risk of recurrence in univariate and multivariate analyses.[11]

The appearance of FTV was characterized by the presence of a collagen matrix layer on the walls of tumor blood vessels.[11] Type I collagen matrix density has been proven in vitro to help cellular remodeling in tumor angiogenesis and vasculogenesis.[12] Microvascular tumors tend to be malformed, thinner, more permeable and more tortuous than blood vessels in normal tissues.[13] This microvascular fragility correlates with increased fibrosis.[14] The main etiology of vascular fibrosis is an increase in the number and activity of myofibroblasts which indicates excessive production of extracellular matrix.

.[15] Vascular endothelial cells may contribute to fibrosis by acting as a source of myofibroblasts through the endothelial-mesenchymal transition.[14,16] Vascular smooth muscle cells transform into myofibroblast-like cells and actively to produce extracellular matrix proteins. Fibroblast cells in pro-fibrotic conditions undergo myofibroblasts transformation and induce deposition of extracellular matrix deposition in the adventitia tunica and migrate to the intima tunica.[15] Fibulin-2 is in the vascular extracellular matrix and plays a role in the migration of vascular smooth muscle cells.[17]

Fibulin-2 is a calcium-bound extracellular matrix glycoprotein. Fibulin-2 plays a role in maintaining the stability and integrity of the extracellular matrix and tissue architecture.[18] In addition, fibulin-2 also can regulate the development of cancers such as breast cancer, lung adenocarcinoma, nasopharyngeal cancer, Kaposi's sarcoma and astrocytomas,[19] and is involved in the physiological regulation of the development of the central/peripheral nervous system and its expression increases at the site of the traumatic central nervous system injury.[20,21] Assesment of fibulin-2 expression in meningioma found that 64% of grade II meningiomas showed more intense immunohistochemical staining than grade I meningiomas.[18] Based on the description above, the aim of this study was to determine the association offibulin-2 expression with histopathological grade and FTV in meningiomas.

METHOD

This research is an observational study with a cross-sectional design. The study population was all meningioma cases that had been diagnosed in three Anatomical Pathology laboratories in West Sumatra, namely the Anatomical Pathology Diagnostic Center, Faculty of Medicine, Andalas University, Dr. M. Djamil Padang Hospital and Ahmad Moechtar Hospital Bukittinggi for January 2019 to December 2020 period there were 120 cases. The research sample was meningioma cases with complete data including age, gender, tumor location, slides and paraffin blocks. Based on the sample size formula, 36 cases of meningioma were obtained

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by simple random sampling and re-evaluated HE slides in the form of histopathological grade and FTV. Van-Gieson staining was performed to confirm FTV.

The assessment of the histopathological grade of meningioma based on the 2016 WHO classification is WHO grade I meningioma, WHO grade II meningioma and WHO grade III meningioma. Based on the risk of recurrence and aggressive behavior, the histopathological grades are grouped into low-risk that is grade I meningioma and high-risk that are grade II and III meningioma.[8] The FTV appearance is if there is a collagen matrix layer on the vascular wall in more than 50% of tumor vessels observed by HE staining and confirmed by van-Gieson staining where it is visible the presence of tumor blood vessels in whole or more than 50% of the vascular walls are stained red examined by two observers. The non-FTV appearance is if not visible collagen matrix layer on the overall or less than 50% of the tumor vascular wall or visible on less than 50% of the vascular tumor. The results of the FTV assessment are FTV and non-FTV.[11]

The paraffin block of the study sample was re-cut for immunohistochemical staining with an anti-fibulin-2 primary antibody at 1:200 dilution (Bioenzy, polyclonal antibody). The immuno-histochemical staining method uses the Bond Polymer Refine protocol, which is carried out with an automatic procedure with a Bond-Max Leica machine at the Anatomical Pathology Laboratory of Dr. M. Djamil Padang Hospital. Semi-quantitative assessment of fibulin-2 expression, namely multiplying the percentage score of the number of cells with the brown color intensity value in the cytoplasm of meningioma cells plus one to produce a Histo-score value with the formula $\sum(I+1)Pi$, where I is the intensity of immunoreactivity (0 to 3+), which is 0: negative, 1: weak intensity, 2: medium intensity 3: strong intensity and Pi represents the percentage of tumor cells stained (0 to 100%). The calculation results will show a minimum score of 0 (negative) and a maximum of 400. The median value determines the cut-off point. For statistical analysis, fibulin-2 expression was divided into low fibulin-2 expression if the computed result were below the median H-score and high fibulin-2 expression if the computed result were above or equal to the median H-score.[22]

Univariate analysis was in the form of descriptive data on meningioma characteristics, namely age, sex, tumor location, histopathology subtype, histopathology grade, FTV presence and fibulin-2 expression. Statistical tests using chi-square will analyze the association between fibulin-2 expression to histopathological grade and FTV in meningiomas. The test results are considered significant if the $p<0.05$ value.

RESULT

The population of this study was 120 cases of meningiomas, and there were 20 cases of exclusion caused by missing/damaged slides and paraffin blocks and incomplete data. Samples that met the inclusion criteria were 100 cases, then a sample size of 36 cases was taken, namely 18 cases of high-risk meningioma and 18 cases of low-risk meningioma which were selected by simple random sampling. The most common cases of meningioma were found in the age group of 41-50 years old, namely 17 cases (47.2%), with the mean age of patients being 46.28 years old±SD 10,628. The youngest age is 12 years old, and the oldest is 67 years old. Women were more affected than men, with a ratio of 2.6:1. The most tumor locations were in convexity, namely 29 cases (80.6%). Atypical meningioma is the most common subtype of grade II meningioma at 15 cases (41.7 %). The three most histopathological subtypes of grade I meningiomas were transitional meningioma 5 cases (13.9%), meningothelial meningioma 4 cases (11.1%) and microcystic meningioma 3 cases (8.3%). The histo-pathological grade, based on the 2016 WHO classification, obtained 18 cases (50.0%) WHO grade I, 16 cases (44.4%) WHO grade II and 2 cases (5.6%) WHO grade III. The presence of FTV (Figure 1) was obtained in 20 cases of meningioma (55.6%). Low fibulin-2 expression was found in 12 cases (33.3%), and high in 24 cases (66.7%). The characteristics of the study sample are shown in table 1.

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Table 1. Clinicopathological characteristics of meningiomas.

Characteristic	frequency (n=36)	%
Age		
Average±SD	46.28±10,628	
11-20 years old	1	2.8
21-30 years old	2	5.6
31-40 years old	5	13.9
41-50 years old	17	47.2
51-60 years old	8	22.2
61-70 years old	3	8.3
Gender		
Man	10	27.8
Woman	26	72.2
Location		
Convexity	29	80.6
Parasagittal	2	5.6
Cerebello-pontin angle	1	2.8
Intradural extramedular	3	8.3
Infratentorial	1	2.8
Histopathological subtypes		
Meningothelial meningioma	4	11.1
Fibrous meningioma	2	5.6
Transitional meningioma	5	13.9
Psammomatous meningioma	2	5.6
Angiomatous meningioma	2	5,6
Microcystic meningioma	3	8.3
Chordoid meningioma	1	2.8
Atypical meningioma	15	41.7
Papillary meningioma	1	2.8
Anaplastic meningioma	1	2.8
Histopathological grade		
WHO grade I	18	50.0
WHO grade II	16	44.4
WHO grade III	2	5.6
Fibrotic tumor vessel		
FTV	20	55.6
Non FTV	16	44.4
Fibulin-2 expression		
Low	12	33.3
High	24	66.7

The results of this study showed that there was no significant association between fibulin-2 expression to histopathological grade of meningiomas with a p>0.05, but meningiomas with high fibulin-2 expression (62.5%) were found to be more at high-risk histopathological grade (WHO grade II and III) compared to meningiomas that express low fibulin-2 (25%) as shown in table 2. The results of immunohistochemical staining of fibulin-2 can be seen in figure 2.

Table 3 shows that the percentage of FTV was found to be higher in meningiomas that expressed low fibulin-2 at 58.3% compared to meningiomas that expressed high fibulin-2 at 54.2%. Statistically, there was no significant association between fibulin-2 expression and FTV in meningiomas with a p>0.05.

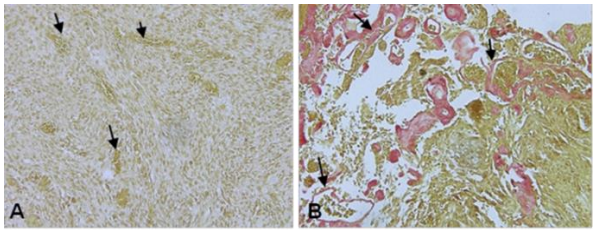

Figure 1. Image of FTV with van-Gieson staining. A. Non-fibrotic tumor vessel, showing thin-walled vessels (arrows) in the meningothelial meningioma. B. Fibrotic tumor vessels, visible the entire wall of blood vessels stained red (arrow) in the atypical meningioma. (A, B van-Gieson stain, 200 times).

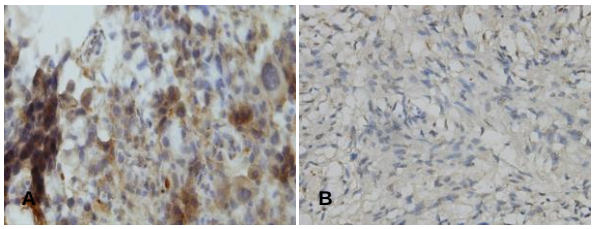

Figure 2. Fibulin-2 expression in meningioma (400 times magnification). A. High fibulin-2 expression is seen in the cytoplasm of tumor cells seen in the papillary meningioma (high risk). B. Low fibulin-2 expression seen in microcystic meningioma (low risk).

Table 2. Association of Fibulin-2 Expression to Histopathological Grade of Meningioma.

Characteristic	Histophological Grade				Total		p-value
	Low risk (WHO grade I)		High risk (WHO grade II and III)				
	F	%	F	%	F	%	
Fibulin-2 expression							
Low	9	75	3	25	12	100	0,077
High	9	37.5	15	62.5	24	100	

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Table 3. Association of Fibulin-2 Expression with FTV in Meningiomas.

Characteristic	Fibrotic tumor vessel				Total		p-value
	FTV		Non-FTV				
	F	%	F	%	F	%	
Fibulin-2 expression							
Low	7	58.3	5	41.7	12	100	
High	13	54.2	11	45.8	24	100	1,000

DISCUSSION

This study showed that the most age group who suffered from meningioma was the age group 41-50 years old, namely 17 cases (47.2%). The average age obtained from this study was 46.28 (SD 10,628), with the youngest age being 12 years old and the oldest age being 67 years old. There were 26 cases (72.2%) female, while 10 cases (27.8%) were male with a female:male ratio of 2.6:1. This is by the literature that incidence of meningioma occurs in the age range of 20-60 years old with a peak incidence of 45 years old.[23] Research conducted by Lakshmi et al (2015) obtained the same result that 30 cases (28.12%) of the 128 cases of meningioma studied were in the age group of 41-50 years old, with more women affected by meningiomas at 94 cases (73.44%) than men 34 cases (26.56%).[24] The same results were also obtained in a study conducted on 70 meningioma patients at Apollo hospital, Dhaka found that the largest age group suffering from meningioma was the age range of 41-50 years old as many as 27 cases (38.6%) with a ratio of women: men of 2.5:1.[25]

Research by Rejeki et al (2019) in West Sumatra for the 2012-2015 period also obtained similar results, namely the most cases were in the age group of 41-50 years old, amounting to 17 cases (45.7%) and regarding women more (91.4%) with a ratio of women and men is 10.7: 1.[4] Similarly, research at dr. H. Adam Malik Hospital, Medan North Sumatra from August 2018-May 2019, the results were that the majority of cases were in the 41-50 age group, with 12 cases (37.5%), while women dominated meningioma sufferers based on gender by 23 cases (71.9%) while men were only 9 cases (28.1%).[26]

The high incidence of meningioma in the age group of 41-50 years old and the female sex is partly due to factors from the use of oral contraceptives and other hormonal contraceptives for the treatment of gynecological diseases or fertility problems consumed for 1-4 years.[27] In addition, meningiomas contain steroid hormone receptors, especially progesterone and estrogen receptors. This female sex hormone plays a role in the tumorigenesis of meningioma. Progesterone receptors are found in 90% of meningiomas, whereas estrogen receptors are found in 40%. The increase in meningioma growth during pregnancy, the relationship between meningioma and breast cancer and the duration of hormonal contraceptive use for 1-4 years are evidence that meningioma is a tumor that is influenced by hormonal.[27.28]

The most meningioma locations in this study were in convexity, which was 29 cases (80.6%). According to the literature, 90% of meningiomas are located on supratentorial sites, namely in convexity and parasagittal.[29] Research by Lakshmi et al (2015) and Karim et al (2016) found convexity to be the most anatomic location for meningioma, with 41 cases (37.27%) and 27 cases (38.6%), respectively.[24.25] Likewise, 238 cases of meningioma found the most locations of meningiomas in convexity, which was 81 cases (31.1%).[30] The location of meningioma tumor is one of the prognostic factors in meningioma because it affects the accessibility of surgery and the involvement of the organ structures around the meningioma tumor determines whether total resection can be performed.[31] In addition, the clinical symptoms arising in the meningioma are related to the location of the tumor due to the mass effect of the tumor that compresses theunderlying organ structures.[32]

Atypical meningioma is the most common subtype of grade II meningioma, with 15 cases (41.7%). Atypical meningioma is a subtype that has increased in incidence since the last review of its diagnostic criteria (WHO classification 2016). The incidence of atypical meningioma reportedly increased by 20-35% of all meningiomas (according to WHO 2016), compared to previously according to WHO 2007 by about 5-7%.[33]

The three most histopathological subtypes of grade I meningiomas are transitional meningioma 5 cases (13.9%), meningothelial meningioma 4 cases (11.1%) and microcystic meningioma 3 cases (8.3%). This is in line with the

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study on 126 meningioma cases at Chandigard Hospital, India, which also found the three most meningioma subtypes, namely transitional meningioma 67 cases (53.2%), followed by meningothelial meningioma, 22 cases (17.3%) and microcystic meningioma 7 cases (5.7%).[34] In contrast to the results obtained in Desai et al (2016) and Lakshmi et al (2015) where the three most meningioma subtypes are meningothelial meningioma 32 cases (64%) and 30 cases (23.44%), psammomatous meningioma 5 cases (10%) and 30 cases (23.44%) and fibrous meningioma 3 cases (6%) and 28 cases (21.88 %).[24.35]

The results of this study indicated that WHO grade I meningioma was the most common, namely 18 cases (50.0%), while grade II meningioma was 16 cases (44.4%) and grade III meningioma was 2 cases (5.6%). In accordance with the literature which states that more than 80% of meningioma cases are WHO grade I, 20-25% WHO grade II and 1-6% WHO grade III. [8] Research by Jansari et al (2020) also obtained the same result, namely 28 cases (93.33%) were WHO meningioma grade I.[36] Likewise the study of Malik et al (2018), Desai et al (2016), and Karim et al (2016) found that meningioma WHO grade I was the most common, namely 108 cases (85.7%), 45 cases (90%) and 63 cases (90%), respectively.[25,34,35]

The presence of FTV was 55.6% (20 cases). Research by Hess et al (2020) showed that 140 of 295 cases of grade I meningioma showed FTV (47.45%). The incidence of FTV at grade I meningiomas in the study strongly correlated with vascular density with p< 0.001 and tumor recurrence.[11] Fibulin-2 expression results were high expression in 24 cases of meningioma (66.7%) and low expression in 12 cases of meningioma (33.3%). The same thing was found in the research of Sofela et al (2021), where meningioma expresses fibulin-2.[18]

High-risk meningioma (WHO grades II and III) in this study had a high fibulin-2 expression of 62.5% compared to low fibulin-2 expression of 25%, while in meningioma low risk (WHO grade I) had a low fibulin-2 expression of 75%. Statistically, there was no significant association between fibulin-2 expression and histo-pathological grade of meningiomas with p=0.077. Not many studies that have discussed fibulin-2 expression in meningiomas, and it is still relatively new. In 2021 there was one study conducted by Sofela et al entitled fibulin-2, a novel biomarker for differentiating grade II meningioma from grade I meningioma. Based on this study, it was found that about 64% of grade II meningiomas express strong fibulin-2 compared to 40% of grade I meningiomas.[18]

This study found no significant association between fibulin-2 expression and histopathological grade. This is possible due to the absence of standard assessments and cut-off values for fibulin-2 expressions available today. Quantitative research is needed to assess the level of fibulin-2 expression, which can be related to the histopathological grade of meningiomas. The assessment of plasma fibulin-2 level using the ELISA method obtained plasma fibulin-2 concentration was significantly higher in grade II meningioma with a p-value=0.03. The determination of the cut off value of plasma fibulin-2 levels was >2.5 ng / mL, which had a specificity of 95% to identify patients with grade II meningiomas compared to grade I meningiomas.[18]

The percentage of FTV was found to be low fibulin-2 expression at 58.3% compared to high fibulin-2 expression at 54.2%. Statistically, there was no significant association between fibulin-2 expression and FTV in meningiomas with p=1,000. To date, no studies have assessed the relationship of fibulin-2 expression with FTV in meningiomas.

The fibulin-2 expression has been immunohistochemically analyzed and expressed highly in patients with pulmonary fibrosis. High levels of fibulin-2 mRNA expression in pulmonary fibroblasts localized on the alveoli and vascular walls.[37] In addition, fibulin-2 as part of the extracellular matrix protein plays, a role in the adhesion, migration and proliferation of vascular smooth muscle cells, that is, by interacting with versican. Fibulin-2 can also be produced by smooth muscle cells in response to injury and regulate the migration of smooth muscle cells during vascular wall repair.[17]

The incidence of FTV in grade I meningioma is closely related to the microvascular density and also found a strong correlation between vascular density and FTV. However, there is no correlation of FTV with the meningioma subtype. Research on the correlation of FTV with high-degree meningiomas (WHO degrees II and III) still does not exist. [11]

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There is a correlation of FTV with tumor recurrence and there is also a correlation of FTV with prognosis.[11] The recurrence rate in some meningiomas cases is associated with tumor vascularization patterns.[9] Grade II and III meningiomas indicate multiple microvascular, while most grade I meningiomas show a few large blood vessels. A significant association (p=0.0002) was found between the grade of meningioma and the vascularization pattern.[38]

CONCLUSION

There was no significant association of fibulin-2 expression to histopathological grade and FTV in meningiomas. Quantitative research with a larger samples is needed to obtain standard values of fibulin-2 expression levels in meningiomas and its relationship to recurrence risk.

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