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H3K27me3 Expression has Association with Histological Grade of Meningioma

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ABSTRACT

Background
Meningioma is the most common primary central nervous system tumor. It has various histological patterns, locations, and grades, and posing challenges in therapy and prognosis. It has a complex tumorigenesis and H3K27me3 epigenetic changes is one of the factors that play a role in meningioma tumorigenesis. This study aims to determine the correlation of H3K27me3 expression with clinicopathological factors in meningioma.

Methods
This study was an analytical observational study with a *cross-sectional* study involving 73 cases of meningioma at Prof. Dr. I.G.N.G. Ngoerah Hospital Denpasar, consisting 36 grade 1 cases, 31 grade 2 cases, and 6 grade 3 cases. H3K27me3 expression was evaluated by immunohistochemical staining and its expression was classified into retain and loss. A chi-square test was done to analyze the relationship between H3K27me3 expression with age, gender, location, and histological grade of meningioma. Significance was determined at $p<0.05$.

Result
In this study, 5 cases (6.8%) showed H3K27me3 loss and were found in 9.7% of grade 2 cases and 33.3% grade 3 cases. Bivariate analysis showed a significant relationship between grade and H3K27me3 expression ($p=0.018$). There was no significant association between H3K27me3 expression and age, gender, and location.

Conclusion
The expression of H3K27me3 is associated with the grade of meningioma. It provides additional prognostic information in conjunction with other clinicopathological parameters.

Keywords: epigenetic, grade, H3K27me3, meningioma

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INTRODUCTION

Meningiomas are the most common primary central nervous system tumours, accounting for 40% of tumours overall. They are mostly benign tumours that can be treated with resection and have good outcome. However, in some cases meningiomas can be aggressive with frequent recurrences. Based on the Central Brain Tumour Registry of the United States (CBTRUS-US) statistical report in 2015-2019, the most common overall brain tumour location was in the meninges (40.2% of all brain tumours).[1–3]

Meningioma is associated with several risk factors including ionizing radiaamtion, obesity, occupation (related to pesticides/ herbicides), hormonal factors, and molecular characteristics.[2,3] Meningiomas typically arise in intracranial, intraspinal, or orbital locations with the most common sites is the cerebral convexities.[1,3,4] Meningiomas are usually low-growing, occurring with neurological deficits that vary depending on tumour location. Clinical signs and symptoms can arise from the compression of adjacent structures.[3]

The diagnosis of meningioma is established based on clinical, radiological, histopathological, and molecular.[1,3,5,6] The World Health Organization (WHO) grading system is the standard for determining the grade of meningioma. It is defined by histological and molecular features. Molecular markers such as the telomerase reverse transcriptase (TERT) promotor and loss of the cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) are prognostically relevant but only present in a small subset of meningioma (mostly anaplastic) meningiomas.[7,8] The 2021 WHO classification classifies meningiomas into grades 1, 2, and 3. Grade 1 is the most common and least aggressive, while grade 2 and 3 are rarer and more aggressive tumors.[1,3,7,9–11]

Epigenetics has a role in meningioma tumorigenesis The trimethylation of lysine 27 of histone 3 (H3K27me) is one of the epigenetics mechanisms.[12–16] Currently, there is still no comprehensive literature on the pathogenesis of meningioma concerning the role of H3K27me3. Loss of expression of H3K27me3 in several literature reviews is known to be associated with poor prognosis of meningioma.[17,18] More research on H3K27me3 expression in meningioma will add information on its role in the prognosis and target therapy of meningioma patients. This study aimed to prove the relationship between H3K27me3 expression and clinicopathological parameters of meningioma.

METHODS

This research was a cross-sectional analytical study. There were 210 meningioma cases underwent surgery in Prof. Dr. I.G.N.G. Ngoerah Hospital between January 2019 and December 2023. According to minimal sample size, 73 cases were included in this study that consist of all grade 2 and grade 3 meningiomas (36 and 6 cases respectively), and the rest (36 cases) were grade 1 meningiomas. The clinical data set included age at diagnosis, gender, tumor location, and histopathological diagnosis were collected from the hospital management information system.

H3K27me3 expression was evaluated by immunohistochemical staining with rabbit monoclonal H3K27me3 antibody C36B11 (1:200, Cell Signaling, Danvers, MA, USA) using an Automatic Leica Bond-Max immunostainer. Immunostaining was done in formalin-fixed paraffin-embedded (FFPE) tissue which retrieved from archive at Anatomical Pathology Laboratory Prof. Dr. I.G.N.G. Ngoerah Hospital.

Interpretation of H3K27me3 expression was using a binocular light microscope Leica DM500 was conducted by the researcher and two pathologists. H3K27me3 expression was assessed in tumour cell nuclei, with endothelial staining as positive internal control. H3K27me3 expression was classified into retained and loss expression. Staining scoring was assessed based on the following three categories: (0) loss ≤5% tumor cells nuclei staining; (1+) partial loss >5-90% tumor cells staining; (2+) full retained >90% tumor cells nuclei staining. Full retained and partial loss staining were then grouped into the retained expression category, while loss staining was grouped into loss expression.[19–21]

Data was processed using the Statistical Package for the Social Sciences (SPSS) 27.0 for Windows. Descriptive analysis to determine the frequency of the characteristics of the subject and chi-square analysis to analyze the relationship between H3K27me3 expression with age, gender, location, and

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histological grade of meningioma. The significance value was determined at p<0.05.

RESULT

Table 1. Subject characteristics.

Parameter	Total	Percentage (%)
Age (median)		
<48 years old	36	49.3
≥48 years old	37	50.7
Sex		
Male	14	19.2
Female	59	80.8
Tumor Location		
Supratentorium		28.8
Convexity	21	15.1
Falx and parasagittal	11	16.4
Suprasellar	12	2.7
Intraorbital	2	28.8
Wing sphenoid	21	8.2
Posterior Fossa	6	
Grade		49.3
1	36	42.5
2	31	8.2
3	6	
H3K27me3 expression		
Retained		42.5
Full Retained	31	50.7
Partial loss	37	6.8
Loss of expression	5	

The age of the patients ranged from 16 to 73 years old, with a mean age of 48.42 ± 7.79 years and median age of 48 years. Female cases were predominant with a female-to-male ratio was 4.2:1. The majority of tumors were located at the supratentorial area, particularly convexity (28.8%) and wing sphenoid (28.8%). Most of the samples in this study (93.2%) were primary meningiomas, while 6.8% were recurrent tumours. Tumor grading was determined by histological grading. Most of the cases were meningioma grade 1 (36 cases; 49,3%), followed by grade 2 (31 cases; 42.5%) and grade 3 (6 cases; 8.2%). Based on H3K27me3 expression, there were 31 (42.5%) full retained cases, 37 (50.7%) partial loss cases, and 5 (6.8%) cases with loss of expression. All clinicopathological characteristics are summarized in Table 1.

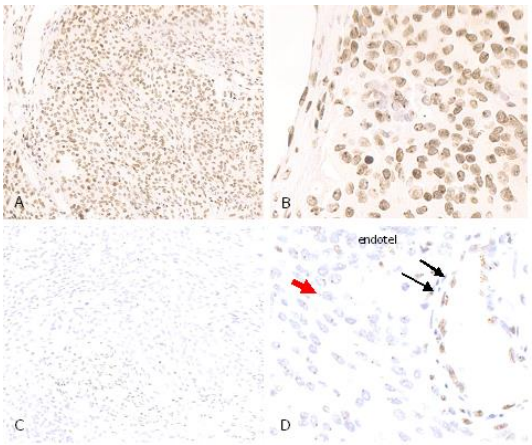

Figure 1. H3K27me3 expression. (A) (B) H3K27me2 with retain expression. More than 90% of tumor cells were stained. (B)(C) H3K27me3 with negative staining in tumor cells (red arrow) and positive in endothelial cells as the internal control (black arrow) (IHC H3K27me3, A.100 times, B.400 times)

In the patients with age <48 years and ≥ 48 years, there was more cases with retained H3K27me3 expression, 94.4% and 91.9%, respectively. A total of 55 (93.2%) out of 59 cases of female patients had retained H3K27me3 expression. A total of 5 cases (6.8%) showing H3K27me3 loss were found in grade 2 (9.7%) and grade 3 (33.3%) meningiomas. Bivariate analysis showed a significant relationship between grade and H3K27me3 expression (p=0.018). Overall, there was no significant association between age, gender, and tumour location with H3K27me3 expression, but there was a significant association between tumour grade and H3K27me3 expression. This can be seen in Table 2.

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Table 2. The association between H3K27me3 expression with age, sex, location, and meningioma grade.

Variable	H3K27me3 expression		Total	*p-value*
	Loss	Retained		
Age				1.000
<48 years old	2 (5.6%)	34 (94.4%)	36 (100%)	
≥48 years old	3 (8.1%)	34 (91.9%)	37 (100%)	
Sex				1.000
Male	1 (7.1%)	13 (92.9%)	14 (100%)	
Female	4 (6.8%)	55 (93.2%)	59 (100%)	
Tumor location				0,051
Supratentorial	3 (4.5%)	64 (95.5%)	67 (100%)	
Posterior Fossa	2 (33.3%)	4 (66.7%)	6 (100%)	
Grade				0.008
1	0 (0%)	36 (100%)	36 (100%)	
2	2 (9.7%)	28 (90.3%)	31 (100%)	
3	2 (33.3%)	4 (66.7%)	6 (100 %)	

DISCUSSION

Recent advances in omics technology (genomics, transcriptomics, epigenomics, and proteomics) with clinical data are a promising methodology for providing highly accurate prediction models for meningioma development, showing potential for early and accurate diagnosis, effective therapeutic strategies, and good prognosis for meningioma.[22,23]

Epigenetic has role in meningioma tumorigenesis. H3K27me is one of the epigenetics mechanisms, in terms of histone modification. H3K27 mediated by EZH2 subunit of the Polycomb repressive complex 2 (PRC2), contributes to chromatin compaction and is related to the silencing of genes.[15,16,19,20,24,25] It is implicated in different cancers including breast, prostate, colon, ovarian, malignant peripheral nerve sheath tumors, ependymomas, and gliomas.[18,26,27] Loss of H3K27me3 expression was shown to be an adverse prognostic factor for progression-free survival (PFS) in grade 1 and 2 meningiomas.[27] There is no clear literature revealing the pathogenesis of meningioma associated with H3K27me3. However, several studies on meningioma examined the epigenetic influence of meningioma, especially regarding the modification of histone H3K27me3 in meningioma. Loss of expression of H3K27me3 in several literature reviews is known to be associated with poor prognosis of meningioma. More research on H3K27me3 expression in meningioma will add information on its role in the prognosis and target therapy of meningioma patients.[28]

In this study, it was found that most of the subjects ranged in age from 40 to 48 years, with a median of 48 years. Based on the literature, meningioma is the most common primary CNS tumours in adulthood with a median age at diagnosis of 66 years, in line with the characteristics of meningioma which most cases are benign tumors, slow growth, often detected in old age, although it can also occur at a younger age.[1–3]

Meningiomas are more common in women than men, which is thought to be related to hormonal factors. Women have a higher propensity to develop meningiomas, especially during peak reproductive years. The incidence rate ratio (IRR) of meningioma between women and men increases with age.[2,3,29–31] Female hormones can modulate cell cycle proliferation and development through transcriptional mechanisms involving receptors. Estrogen has been established as one of the hormones involved in the genomic instability of cells. Estrogen also interacts with insulin growth factor (IGF), which stimulates tumor growth and prevents cell apoptosis.[30]

Meningiomas may present at intracranial, intraspinal, or orbital locations. The most common locations include cerebral convexity. This is in line with what is obtained from this study where the most common location is in the convexity area. The location of the tumor may be related to the symptoms. Clinical signs and symptoms may result from pressure on adjacent structures.[3]

Meningioma grade 1 is the most common and least aggressive, grade 2 and 3 are rarer and more aggressive tumors. In many studies on meningioma, it is found that the most common case of meningioma is grade 1 meningioma followed by grade 2 and grade 3 as the least cases.[1,2,32,33] This is in line with that obtained in this study, which is 49.3% consisting of grade 1 meningioma; 42.5% for

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grade 2, and 8.2% for grade 3, although not all grade 1 cases is involved in this study. Most of the samples in this study (93.2%) were primary meningiomas, while 6.8% were recurrent tumours. The recurrent tumour samples were grade 2. From several publications, higher-grade meningioma tumours increase the risk of recurrence.[34]

Variability in the outcome of patients with meningioma based on standard classification is a clinical challenge. Several clinicopathological factors have been influencing meningioma outcomes including tumour grade, location, gross total resection (GTR), and molecular factors such as TERT and CDKN2A/B promoter mutations.[3,35]

Age has a great influence on survival after being diagnosed with malignant or non-malignant meningioma.[32,36] In this study, H3K27me3 expression did not have a significant relationship with age. This is supported by the findings in several previous studies.[18,19,28] Although the incidence of meningioma is higher among women, gender is not considered a factor associated with H3K27me3 expression. Studies are showing that there is no relationship between gender and prognosis.[35]

The challenging location of the tumor causes difficulty in the surgical/GTR procedure for meningioma sites that are difficult to access, leading to faster recurrence as there is still residual tissue that has not been removed. This poses a challenge to doctors despite the benign nature of these tumors. As symptoms and treatment strategies are highly site-dependent, it is important to analyze the role of tumor location in the clinical examination of meningiomas.

Meningioma grade is associated with the risk of recurrence and overall survival and influences therapy selection. 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.[1] The most common meningiomas are grade 1, benign, and resolved after extensive surgical resection. Grade 2 meningiomas represent nearly 5-15% of cases, and nearly 1-3% are grade 3.[37]

Bivariate analysis showed a significant relationship between grade and H3K27me3 expression. Recently, there has been interest in investigating the role of other epigenetic changes, such as histone modifications in meningiomas, particularly clinically aggressive or higher-grade meningiomas.[26] H3K27me3 is histone modification linked to gene repression and plays an important role in mediating the expression of genes involved in lineage and differentiation. In pediatric posterior fossa ependymoma, low H3K27 methylation is associated with a higher grade. An Enhancer of Zeste Homologous Inhibitory Protein that directly inhibits the EZH2 subunit of PRC2, contributing to dysregulated gene crosstalk that drives tumorigenesis. The H3K27M mutation and associated decrease in genome-wide H3K27 trimethylation is also a hallmark of pediatric high-grade gliomas, resulting in elevated MYCN and increased NOTCH pathway gene expression that promotes oncogenesis.[19,26,38–40]

Katz et al (2020) revealed that H3K27me3 loss was a predictor of worse RFS in grade 2 tumours, but not in grade 3 meningiomas.[26,27] Stratification of H3K27me3 loss across clinical variables revealed important trends linking this marker to more aggressive tumours. While the combined prevalence of H3K27me3 loss in meningiomas was 16%, there were significant differences across WHO grades. Meningiomas grade 3 showed approximately six times the prevalence of loss of H3K27me3 expression compared to meningiomas grade 1 (37% versus 6%). The heterogeneity in the combined prevalence of H3K27me3 loss is likely due to the different WHO grades within each study sample population, as the percentage of grade 3 meningiomas included ranged from 0 to 100%. Other clinical variables that signaled aggressiveness also showed a significant prevalence of H3K27me3 loss, including recurrent meningiomas and primary meningiomas with adjuvant radiotherapy. [21]

The Tübingen study found H3K27me3 expression loss in a smaller proportion (4.7%) of meningiomas, with an increased rate of H3K27me3 expression loss in tumors with higher grade (3.1% for grade 1, 10.4% for grade 2, 17.7% for grade 3). In the Tübingen study, it was found that H3K27me3 expression loss was significantly increased in recurrent meningiomas.[19] Katz et al. (2020) revealed that H3K27me3 loss was a predictor of worse RFS

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in grade 2 tumors, but not in WHO grade 3 meningiomas.[26,27] Stratification of H3K27me3 loss across clinical variables revealed important trends linking this marker to more aggressive tumors.

Based on the findings in this study as well as various previous studies concerning the role of H3K27me3 as a prognosis factor and potential target therapy in the future, it is expected to provide a personalized approach to meningioma case management.

CONCLUSION

Based on the results of this research, it can be concluded that H3K27me3 expression is associated with histological grade of meningioma. The results of this study prove that H3K27me3 expression provides additional prognostic information besides other clinicopathological parameters.

Consensus on preanalytical and analytical is important to gain benefit from H3K27me3 testing. Prospective and multicenter study is needed to test its prognostic and predictive role.

Research Ethics

This research has received approval from the Research Ethics Committee of the Faculty of Medicine, Universitas Udayana with no. 0189/UN14.2.2.VII.14/LT/2024.

Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this research.

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