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Original Research Article

Histomorphological spectrum of meningeal tumours and its association with MIB-1 labelling index

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ABSTRACT

Background: Meningiomas are extremely common, slow growing tumours originating from meningeal covering of brain and spinal cord. They are mostly encountered in middle or later adult life. Females are affected more commonly than males. Grading of meningiomas based on histological features has certain limitations in predicting exact biological behavior hence ancillary studies like immunohistochemistry can be used to predict the nature of the lesion.
Methods: This prospective cross-sectional study was conducted in pathology department in our institute. Total 105 cases, diagnosed as meningioma between October 2019 to May 2021 were included in the study. Immuno-staining was performed using MIB-1 antibody against ki67 antigen. Various statistical test methods like chi square test, unpaired t test and spearman's rho correlation were used to evaluate the significant value.
Results: Among 105 patients analysed there were 78.09% females (mean LI 4.01±3.25%) and 21.91% males (mean LI 3.17±2.64%). Mean age of presentation was 53.14 years and most common subtype was transitional meningioma with 51.43% cases. Histological grading revealed 95.24% WHO grade 1 tumor (mean LI- 3.33±2.22%), 4.76% WHO grade 2 (mean LI- 13.80±2.28%) and no case of WHO grade 3. There was correlation between values of MIB-1 LI and histological grade. Some differences for MIB-1 labelling index were found among the subtypes of meningioma of same grade.
Conclusions: The MIB-1 is one important tool in addition to routine histological evaluation. High MIB-1 LI indicates higher grade of meningioma.

Keywords: Histologic grade, Ki67, Meningioma, MIB-1

INTRODUCTION

Meningioma so named by Harvey Cushing in 1922, is a group of heterogeneous tumors that arise from meningothelial cells. Meningiomas are predominantly benign tumors usually attached to duramater which are thought to derive from arachnoid cap cells in meningeal coverings of spinal cord and brain.[1] Meningiomas (benign) are recognized by their histological subtype and lack of anaplastic features.[2] Morphologically, meningiomas are heterogenous and several histological types of them are described. Of more clinical significance is the histological grade which corresponds to benign/ aggressive nature of tumour. Atypical meningioma is intermediate grade tumor between benign and malignant (Table 1).[3,4]

Meningiomas produce neurological signs and symptoms due to compression of adjacent structures: and the specific deficit depends on tumor location. Headache and seizure are common nonspecific presentations.[5] Meningiomas constitute 30% of primary intracranial tumors. They are generally slow growing benign tumors with predilection for women.[6] Various parameters taken into consideration for histological grading include cellularity, mitotic index, sheet like or small cell pattern,

macronucleoli with nuclear pleomorphism and tumour necrosis.[7] According to world health organization (WHO) criteria meningiomas are classified into 3 grades. Grade I meningiomas are most frequent and benign with low risk of recurrence. Grade II meningiomas are less common with higher rate of recurrence and grade III tumors are rare.[8] The WHO classification aims to better predict the clinical behavior with the histological grading system.[9] Traditionally, CNS WHO tumor grades were written as Roman numerals. However, recent classification of WHO have emphasized more uniform approach of grading and have favored the use of Arabic numerals for grading, as is currently done for all other organ system.[10]

Table 1: WHO 2021 Histomorphological criteria for grading of meningioma.[4]

WHO Grade	Criteria
Grade-1	Mitosis <4/10 hpf
Grade-2	(a) Mitosis 4-19/10 hpf (b) Brain invasion (c) 3 or more of following five features 1.Increased cellularity 2.Uninterrupted pattern-less or sheet-like growth 3.small cell with a high nuclear/ cytoplasmic ratio 4. prominent nucleoli 5.Foci of spontaneous necrosis
Grade-2	Overtly malignant cytology (resembling carcinoma, melanoma or high grade sarcoma) and markedly increased mitosis >20 mitosis/10 hpf

Grading system based on histopathological features has certain limitations in predicting the exact biological behavior of meningioma. Hence the use of ancillary techniques is necessitated to predict tumor growth and recurrence. Amongst the various techniques available to measure cell proliferation, Ki67 is the most widely used immunohistochemistry marker.[8]

The MIB-1 monoclonal antibody has been used frequently to stain Ki67 antigen, which is present in all proliferative cells, in order to investigate the growth potential of systemic and intracranial neoplasm. MIB-1 labelling index (LI) would reflect tumour proliferating potential, the high levels of which represent increased tumor proliferation.[11]

Ki67 is a nuclear protein associated with the mitotic activity that functions as a marker for cell proliferation index (CPI) and is present in all phases of cell cycle, except the G_0 phase. This protein has been shown to be effective at determining the CPI in meningiomas.[12] The nuclear protein Ki67 is an established prognostic and predictive indicator for assessment of biopsies from patients with cancer. There is correlation between the ratio of Ki67 positive malignant cells and patient survival. Ki67 may be promising factor for targeted molecular therapies.[13]

The Objective of this study was to grade meningeal tumours according to current WHO grading criterion which is based on histomorphology and to evaluate the association of these histological features with MIB-1 labelling Index.

METHODS

Study setting

This Cross -sectional hospital based study was conducted in department of pathology, S. N. Medical College Agra. One hundred five specimens of meningeal tumors received from neurosurgery after surgical resection in the department of Pathology in S. N. Medical College Agra and other hospitals were included in the study. Duration of study was October 2019 to May 2021.

Inclusion and exclusion criteria

Inclusion criteria was radiologically and histopathologically diagnosed cases of meningeal tumors and specimen which were inadequate, autolysed and with incomplete medical records were excluded from the study.

Histopathological evaluation

Specimen received in department of pathology were immediately fixed in 10% buffered formalin. Routine H and E stained paraffin sections was studied under following parameters: age and sex distribution, anatomical location of tumor, histological subtypes, histopathological features, and WHO grade of tumor mitotic figures were assessed in the areas of high mitotic activity by taking average of ten consecutive non overlapping high power field. The six representative histologic parameters evaluated were: increased cellularity, number of mitotic figures, sheeting, small cell change, necrosis and brain invasion. Each parameter was evaluated as present or absent.

MIB1 staining index

After the study of Haematoxylin and Eosin stained slides, Immunohistochemistry was performed on newly cut section. Immunohistochemical reaction was performed by the bioptin-streptavidin method using MIB-1 mouse MoAb which recognises an epitope on Ki67. Antigen unmasking in paraffin sections was performed by autoclaving pretreatment. After being deparaffinized and rinsed with tap water, the sections is immersed in a stainless-steel vessel filled with 0.01 M citrate buffer (pH 6.0) and autoclaved at 120°C for 10 minutes. The section then was incubated with 0.3% hydrogen peroxide in methanol to block the endogenous peroxide. After being

washed with tap water and TB (50 mM tris-hydrochloric acid buffer pH 7.6) the sections were incubated overnight at 4°C with the MIB1 antibody (1:100) in TTBS (25 mM tris-HCl (pH7.6), 0.05% tween 20 and 0.5 M sodium chloride) containing low fat milk. After being rinsed twice with TTB (50 mM TB plus 0.1% triton ×100) and once with TB, the sections were incubated for 30 minutes at room temperature with anti-mouse immunoglobulin G (1:200) in TTBS containing with 5% low fat milk. After being rinsed twice with TTB and once with TB, the section was incubated for 30 minutes at room temperature with streptavidin-horseradish peroxide conjugate (1:300) in TB. Hematoxylin was used for counterstaining. Negative controls were obtained by omitting the primary Antibody. The percentage of MIB-1 positive cells was determined by examining 40 high power field in representative areas of surgical materials over 1000 tumor cells. In cases of heterogenous distribution of labelled cells, the areas with highest density of MIB1-staining nuclei were regarded as area of proliferative activity of the tumor. In tumors with infrequently labelled cells the percentage were expressed as less than 0.1.31

Histomorphological features

Brain infiltration defined as irregular, tongue like protrusion of tumor cells infiltrating underlying brain parenchyma without an intervening layer of leptomeninges. Brain invasion has been included as single criterion for grading tumors directly as atypical meningioma (grade-2).[4,17] It was registered as either present, absent or inaccessible.

Hypercellularity is considered when >53 nuclei/high power field (HPF).[3,14,15]

Sheeting defined as lack of typical meningioma growth pattern i.e. loss of whorled or fascicular pattern, noted as present when covered more than half of the field of vision at 10x (low power) magnification.[3,14,15]

Macronucleoli present when easily observed with 10x magnification.[3,14,15]

Small cell formation when tumour cells showed increased nuclear cytoplasmic ratio (lymphocyte like morphology).[3,14,15]

Statistical analysis

The statistical analysis done in this study was chi square, unpaired t test and Anova using SPSS 21. Spearman's rho correlation between mitosis and MIB-1 LI was done. P value <0.05 was considered significant.

RESULTS

Total number of 105 meningioma cases diagnosed between October 2019 to May 2021 were included in this study for histopathological and Immunohistochemical analysis.

Table 2: Case distribution, MIB-1 LI and (p value <0.05 significant) on the basis of gender, subtypes, location, and grade.

Variables	No. (n=105)	LI±SD (S)	P value
Gender			
Female	82 (78.09)	4.04±3.25	0.203
Male	23 (21.91)	3.17±2.64	
Subtypes			
Meningothelial	21 (20)	3.24±2.72	0.09
Fibrous	09 (8.57)	2.44±1.24	
Transitional	54 (51.43)	3.61±2.21	
Metaplastic	02 (1.90)	3.00±1.41	
Psammomatous	03 (2.86)	2.67±1.15	
Angiomatous	07 (6.67)	2.14±0.90	
Microcystic	04 (3.81)	3.00±2.95	
Atypical	05 (4.76)	14.40±2.28	
Location			
Convexity	47 (44.76)	4.53±3.86	0.089
Transtentorial	15 (14.29)	2.80±1.66	
Parafalcine/falx	19 (18.1)	3.90±2.31	
Cerebellar	01 (0.09)	14.00±0.00	
Posterior Fossa	07 (6.67)	2.14±1.35	
Sellar	02 (1.90)	1.50±0.71	
Olfactory groove	02 (1.90)	2.00±0.00	
Spinal cord	05 (4.76)	4.00±1.58	
Others	03 (2.86)	2.00±1.73	
Grade			
WHO Grade 1	100 (95.24)	3.33±2.22	0.0001
WHO Grade 2	05 (4.76)	13.80±2.28	

Among these, female preponderance was seen with female to male ratio of 3.57:1. The correlation of gender to MIB-1 LI was statistically insignificant (p value >0.05). There was also a female predominance in grade-1 meningioma with 77 (73.33%) cases, 23 (21.90%) cases in males. No case of grade-2 meningioma was seen in males, whereas all 5 (4.76%) cases of grade-2 were in females. Most of the cases, 26 (24.76%) were seen in 41-50 years age group, followed by 23 (21.90%) cases in 51-60 and 22 (20.95%) cases in 60-70. There were 15 (14.29%) cases in 70-80 years of age group, 14 (13.33%) cases in 31-40 years and 5 (4.76%) cases in 21-30 years age group, respectively. Among females most common age group of presentation was 41-50 years with 24 (22.86%) cases and males presented predominantly in 60-70 years age group with 9 (8.59%) cases. The mean age of presentation for all cases was 53.14 years. For male and females mean age for presentation was 60.87 years and 50.53 years respectively. Site for incidence of meningioma in this study was convexities of brain parenchyma. MIB-1 labelling index was found to be statistically insignificant (p value >0.05) for location. However, convexity had 43 (40.95%) cases of grade-1 and 04 (3.81%) cases of grade-2 which was statistically

significant for histological grade (p value >0.05) while for other sites it was not significant (Table 2).

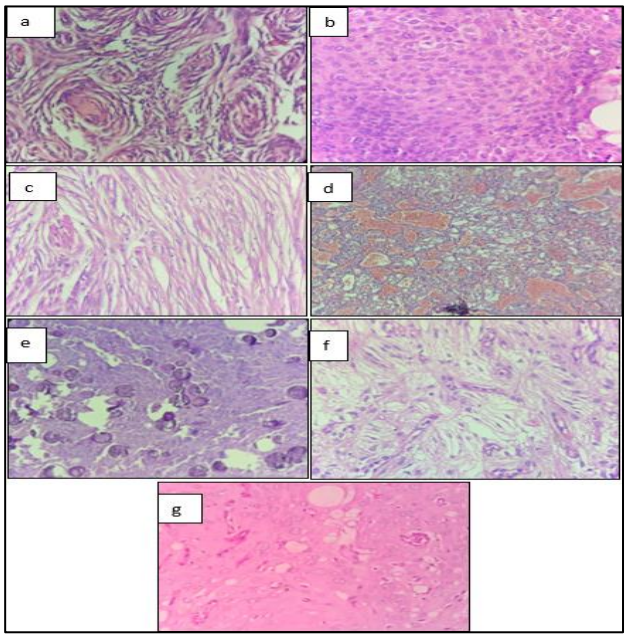

Figure 1: Histomorphology of: a) transitional meningioma (H and E, 400X); b) meningothelial meningioma (H and E, 400X); c) fibrous meningioma (H and E, 400X); d) angiomatous meningioma (H and E, 400X); e) psammomatous meningioma (400X); f) microcystic meningioma (H and E,400X); g) metaplastic meningioma (H and E, 400X).

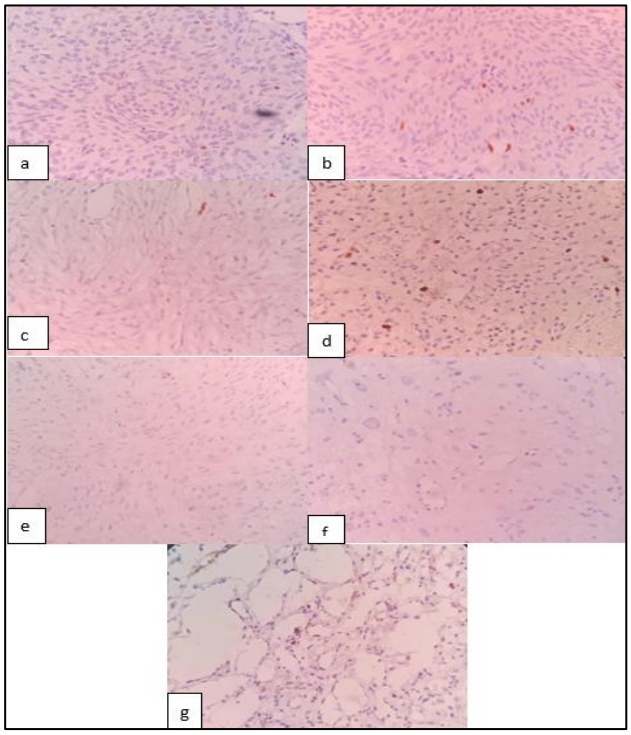

Figure 2: MIB-1 labelling index of grade 1 meningioma (a-g) <4%, (Immunohistochemistry, 400X).

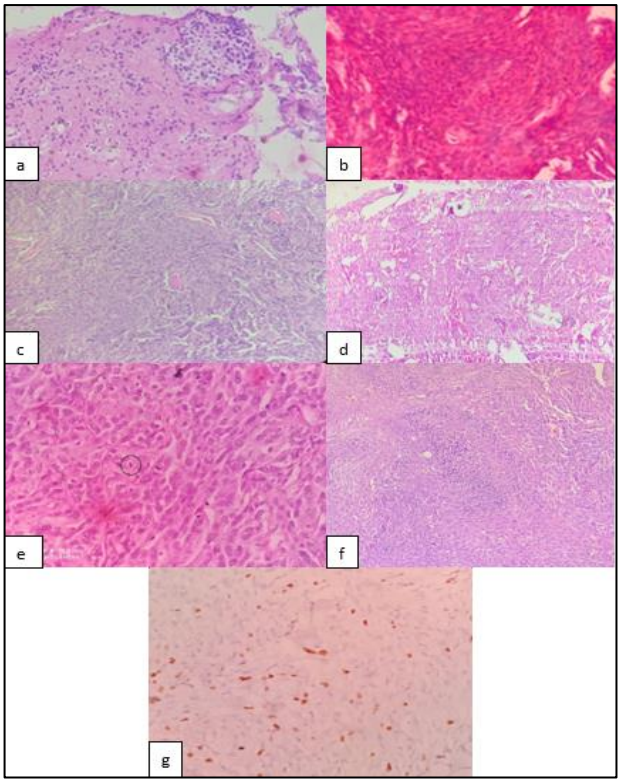

Figure 3: Histomorphological features of Grade 2 Meningioma and It's MIB-1 Labelling Index (a) Brain Invsion (H&E, 400X); (b) small cell change (H&E, 400X); (c and d): sheeting (H&E,400X); (e) Mitosis 4-19/10hpf (H&E, 400X); (f) Necrosis (H&E, 400X); (g) MIB-1 LI 14% (Immunohistochemistry, 400X).

Table 3: Statistical correlation of mitosis and MIB-1 labelling index using spearman's rho correlation.

Mitotic index/10hpf	Minimum	Maximum	Mean	SD
Grade 1 (LI: 3.33±2.22)	0	3	0.81	0.96
Grade 2 (LI: 13.80±2.28	6	12	9.00	2.24
Spearman's rho correlation	Mitosis MIb-1 LI	R=0.435 p(two tailed)=0.00	Statististically significant	

There were, 54 (51.43%, LI: 3.61±2.21) cases of transitional meningioma, 20 (20%, LI: 3.24±2.71) cases of meningothelial meningioma, 9 (8.57%, LI: 2.44±1.24) cases of fibrous meningioma, 2 (1.90%, LI: 3.00±1.41) cases of metaplastic meningioma, 3 (2.86%, LI: 2.67±1.15) cases of psammomatous meningioma, 7 (6.67%, LI: 2.14±0.90) cases of angiomatous meningioma, 4 (3.81%, LI: 3.00±2.95) cases of microcystic meningioma and 5 (4.76%, LI: 14.4±2.28) cases of atypical meningioma (Figures 1 and 2).

The statistical correlation of mitosis and MIB-1 LI using spearman's rho test showed significant association to each other (Table 3).

Five histological parameters were evaluated which were useful in grading of meningiomas. Of all these histological parameters brain invasion, macronucleoli, small cell change and necrosis were statistically significant (p value <0.05). However, sheeting was seen to be insignificant in this study (Table 4, Figure 3).

Table 4: Histological parameters and correlation with grade of meningioma.

Histological characteristic	Recorded as	Total cases (n=105)	WHO grade I (n=100)	WHO grade II (n=05)	P value
Hyper cellularity	Present/Absent	18	15	03	0.058
Sheeting	Present/Absent	26	24	02	0.551
Brain invasion	Present/Absent	04	00	04	0.000
Macronucleoli	Present/Absent	12	09	03	0.008
Small cell change	Present/Absent	09	07	02	0.036
Necrosis	Present/Absent	06	04	02	0.005

DISCUSSION

Meningiomas are extremely common tumors originating from meningeal coverings of the brain and spinal cord. Histopathological examination and grading of meningioma give valuable prognostic information.[20] Our study showed clear predominance of females with 78.09% of total cases which is similar to other studies like Solanke et al, Ghanghorian et al and Raza et al.[3,6,9] The mean age of presentation in our study was 53.14 years and majority of cases (24.76%) fall under 41-50 years age group which was similar to Niranjan et al, Babu et al, Grondahl et al, and Pala EE et al.[5,8,14,15]

This study points out that WHO grade-1 tumors are commonest to occur with female sex predilection which is found similar to majority of studies.[1,3,15] In our study, all cases of grade-2 tumors were females and no case of grade-2 meningioma was reported in males.

This study showed that meningioma commonly occurs in intracranial location with 100 cases and convexity being the most favored site with 47 cases (44.76%). Babu et al, Pala et al, and Telugu et al also had similar results while Magill et al showed skull base as common site in their study.[8,15,21,26]

Brain invasion is defined as irregular tongue like protrusion of tumors into brain parenchyma without leptomeninges. Brain invasive meningiomas are equivalent to grade-2 meningiomas according to WHO 2016 classification.[17] In our study brain invasion was positively correlated with grade of meningioma and MIB-1 LI. The feature like sheeting, necrosis, macronulcleoli and small cell change were seen more frequently in grade-2 tumors. This result is similar to Solanke et al.[3] However, Devprastha et al showed poor correlation with necrosis and brain invasion.[24]

In this study, transitional meningioma was commonest variant with 51.2% cases followed by meningothelial meningioma with 21 (20%) cases and fibrous meningioma 9 (8.57%) cases which is similar to Babu et al and Grondahl et al who also reported transitional meningioma as commonest variant.[8,14] It is different from other studies like Gadgil et al, Telugu et al, Roser et al and Hashemi et al in which meningothelial meningioma was commonest variant.[1,21,23,25]

Mitotic Index was also evaluated in the study. Mitotic index in atypical meningiomas was higher than grade-1 meningiomas and it was positively correlated with MIB-1 LI. This is in accordance with Solanke et al, Carvalho et al, Nilkanthe et al and Devprastha et al.[3,12,22,24]

This study showed 100 (95.24%) grade-1 meningioma, 05 (4.76%) cases of grade-2 and no case of grade-3 meningioma. It is in accordance with study of Solanke et al and Nilkanthe et al which also didn't had any case of grade-3 meningioma and incidence of grade-1 meningioma was higher than grade-2 meningioma.[3,22] Pala et al reported only one case of grade 3 meningioma.[20]

Subjective methods like mitotic index, necrosis etc are still used in determining the grade and proliferating activity of CNS tumors. However, inter-observer differences and sampling errors usually cause problems. The proliferative potential of meningiomas has been studied using the MIB-1 immunohistochemistry in several studies.[3] In study of Roser et al MIB-1 LI in WHO grade I meningioma was 3.54%, WHO grade II meningioma was 11.9% and WHO grade III meningioma was 18.2%.[23] Karabgali et al reported MIB-1 labelling index in WHO grade I meningiomas as 2.23±2.31, WHO grade II meningioma shows 6.53±5.3 and WHO grade III meningioma shows 11.1±7.8.[11] Telugu et al studied Ki67 LI in meningioma cases and reported Ki67 LI in grade I meningioma 3.1% and grade II meningioma show 7%.[21]

Pala et al reported mean Ki67 proliferation index in grade I meningiomas 2% whereas 7.4% in atypical meningiomas.[15] All of these studies showed increase in MIB-1 labelling index according to histological grade. Present study showed MIB-1 LI of 3.33% in grade-1 meningioma and 13.8% in grade-2 meningioma, which is in accordance with the above quoted studies. There was correlation between values of MIB-1 LI and histological grades although MIB-1 LI was of different values in different variants according to gradual differences among these variants. Grade-2 meningiomas had higher MIB-1 LI than grade-1 meningiomas which is in accordance with other studies.

This study was able to provide satisfactory results however there were few limitations like analysis of Mitotic figures are subjective hence their values can have interobserver variations. Various mimickers of mitosis like, apoptotic bodies, lymphocytes, darkly stained nuclei, dying or crushed cells and artefacts, can be mistaken as mitotic figure.

Although MIB-1 labelling index is a one of the commonly used, economical and easily available biomarker for predictive and prognostic and at times therapeutic purposes, however it has its own limitations. MIB-1 labelling index like any other biomarker show interindividual and intraindividual variability i.e. they show differing values for spectrum of patient and differing scores by histopathologist providing MIB-1 measurements respectively. Also, they are not always absolute in their predictive evaluation. Our study also had two cases of recurrent meningiomas, both of which were of grade-1 with low MIb-1 labelling index. However, number of cases were low, hence they were not correlated with other parameters.

CONCLUSION

This Prospective correlational study was done from October 2019 to May 2021.The number of meningioma cases studied was 105 in number. Meningioma was found most commonly in females with female:male ratio of 3.57:1. Mean age of presentation was 53.14 years. Most common age group for meningioma was 41-50 years with 26 (24.76%) cases. Histopathologically most common subtype of meningioma was transitional meningioma with 54 (51.43%) followed by meningothelial meningioma with 21 (20%) cases and fibrous meningioma with 9 (8.57%) cases. There was predominance of grade-1 meningioma with 100 (95.24%) cases, and grade-2 meningioma cases were 05 (4.76%). MIB-1 LI in grade-1 meningioma was 3.33% and in grade-2 meningioma was 13.8% respectively, showing its positive correlation to grade of tumor. Histomorphological changes such as sheeting, necrosis, macronucleoli, small cell change, mitosis and brain invasion was found to be positively correlated to tumor grade. MIB-1 immunostaining yielded credible results in our study. Therefore MIB-1 LI in patients with meningioma of different grades may be a good prognostic and diagnostic marker in parallel to WHO grading criteria. However, further studies with larger sample size maybe required for confirmation and validation of data.

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