Meningioma Prognostic Tool Based on Correlation of Histopathological Grading and Immunohistochemistry

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Abstract

Objectives: Meningiomas are slow-growing brain neoplasms with an inherent trend to recur locally. Although their morphologic grading is simple it does not always correlate with the patient outcome. The fifth edition of the WHO Classification of Tumors of the Central Nervous System (CNS) classifies meningiomas into three grades based on various morphological criteria. Now it is stressed that regardless of the underlying subtype, the criteria defining atypical or anaplastic (i.e., grade 2 and 3) meningioma should be implemented due to greater chance of recurrence compared to the typical CNS WHO grade 1 meningioma. The aim of the present study is to evaluate the status of estrogen receptor (ER), progesterone receptor (PR) and proliferation marker Ki67/MIB-1 in various grades of meningioma in patients.

Methods: A total of 276 cases were included in our study. All archival hematoxylin and eosin (H&E) stained slides were reviewed and regraded according to WHO 2021 criteria. Immunohistochemical analysis for ER, PR and Ki67 was performed on all grade 2 and grade 3 meningiomas and 30 cases of grade 1 formalin- fixed, paraffin- embedded samples.

Results-Out of the total cases, 231 were grade 1 (83.7%),34 were grade 2(12.3%) and 11 were grade 3 (4%).ER was positive in 26% of grade 1 tumors, 5.8% of grade 2 tumors and 0% of grade 3 meningiomas. PR were positive in 70% of grade 1 tumors,20% of grade 2, and 18% of grade 3 tumors. Ki-67/MIB-1 labeling index (LI) was 2.1 in grade 1 tumors, 6.3 in grade 2 tumors and 13.4 in grade 3 tumors. For both PR, Ki-67, differences between grade 1,2 and 3 tumors were significant ($p < 0.001$). There was a reverse relationship between the mean of Ki67 LI and PR status, with increasing grade of tumor.

Conclusions: Ki-67/MIB- 1 LI has a statistically significant positive correlation with the grade as well as with recurrence. It is a helpful auxiliary method for the routine assessment of meningiomas, especially those with borderline atypia. The expression of PR, on the other hand, is a positive prognostic indicator and has a substantial correlation with histological grade. In cases of subtotal resection, high proliferative rate, or recurrence, particularly in cases where the histopathology is borderline, the Progesterone receptor (PR) status in combination with the MIB -LI can offer more insight into the behaviour of a meningioma and act as a prognostic tool for predicting the tumor's recurrence.

Keywords: ER, Ki-67, Meningiomas, MIB-1, PR.

Introduction

Meningioma accounts for around 37.6% of primary CNS (central nervous system) tumours and nearly 50% of benign brain tumours, making it the most prevalent primary CNS tumour.[1] Meningiomas develop in the meningeal layers of the brain or spinal cord with a female-to-male ratio of 2.3 and the average age of presentation is 66 years.[1,2] The WHO 2021 classification categorizes meningiomas in three-tier system (Grade 1,2,3) similar to the earlier WHO 2016 classification.[3] Due of the excellent spatial resolution and contrast of soft tissues, magnetic resonance imaging (MRI) is a useful diagnostic method in oncology.The diagnosis and evaluation of brain tumours can benefit greatly from using MRI sequences, although these sequences are ineffective for differentiating between different

types or grades of tumours.[4] Meningiomas have an inherent trend to recur.[5] Recurrence after apparently complete removal represents one of the most relevant problems of meningioma surgery.[6] According to the WHO 80–81% of meningiomas are categorised as grade 1 or typical. While 1.7% of them are anaplastic or grade 3 meningiomas and 17 to 18% of them are atypical or grade 2 meningiomas.[1,2] The meningioma recurrence rate can increase to 20% after ten years.[7] Higher-grade meningiomas have been documented to have high recurrence rates. The recurrence rate in grade 3 ranges from roughly 50 to 94%. In contrast, the recurrence rate in grades 1 and 2 is 7 to 25% and 29 to 52%, respectively.[8] Apart from the known conditions and risk factors for recurrences like histological malignancy grade and subtotal resection, additional factors like young age, specific histological subtypes, and high proliferative rate also play an important role.[9]

A high mitotic index has been generally considered to be a strong indicator of tumor recurrence.[10] The MIB-1 monoclonal antibody has been used frequently to stain Ki-67 antigen, to investigate the growth index of various systemic and intracranial neoplasm. In astrocytic tumours, the monoclonal antibody Ki-67/MIB-1 is frequently employed and has demonstrated prognostic and diagnostic power.[11] A nuclear antigen called Ki-67 is expressed in the cell cycle's G1, S, G2, and M stages. This nuclear antigen is expressed by proliferating cells throughout the whole cell cycle, and the monoclonal antibody MIB-1 can identify it. The MIB-1 labelling index (L1) is the proportion of immunopositive cells.[11,12] Meningiomas with indices >4% have an increased risk of recurrence similar to atypical meningioma, whereas those with indices >20% are associated with death rates analogous to those with anaplastic meningioma.[13] High Ki-67/MIB-1 labeling index (LI) is associated with a high recurrence rate in meningioma.[14]

The relation between sex hormone receptors and meningiomas has been the subject of several studies.[15-18] The higher incidence of meningiomas in women, their growth during pregnancy and luteal phase with a subsequent decrease after delivery, and their association with breast carcinoma suggest that this type of tumor could be hormone-dependent.[19] Expression of PR by meningioma cells is prognostically a favorable sign while the absence of PR expression would be accompanied by a more aggressive tumoral behaviour.[20] Thus the expression of PRs may relate to tumor grade and recurrence. There is a significant correlation between negative PR status and high MIB-1 LI.[21] The absence of PR, and high mitotic index, as well as tumor grades, are significant factors in assessing disease-free survival.[22] The research data that look at the function of different prognostic indicators in meningiomas is limited to very few. Hence, this study was undertaken to determine the immunohistochemistry expression of hormone receptors and proliferation markers in meningiomas and correlating them with the grade of meningioma and its recurrence.

Methods

This collaborative study was conducted at a tertiary care center of Jammu and Kashmir, North India in the Department of Pathology and Neurosurgery. A total of 276 cases were included in our study which included retrospective data for 8.5 years and prospective cases for 1.5 years. . Relevant paraffin-embedded blocks were taken out and from each block 4 sections of 3-micron thickness were taken. One section was stained with hematoxylin and eosin for revision of the histopathological diagnosis and the remaining 3 sections were stained immunohistochemically. A heat-induced approach using a pressure cooker and Tris ethylenediaminetetraacetic acid pH 9.0 was used for antigen retrieval. Hydrogen peroxide (H2O2) at 3% inhibited endogenous peroxidase activity. Sections were cleaned in Tris buffer (pH 7.6) and then incubated for 30 min at room temperature with rabbit monoclonal primary antibodies against ER (clone SP1, Ventana) and PR (clone 1E2, Ventana). With interim washes in Tris buffer (pH 7.6), the slides were then treated with poly-HRP reagent and diaminobenzidine chromogen. ER- and PR-positive invasive ductal carcinoma of the breast was utilised as a positive control and a negative control by omitting the main antibody. If the tumour cells had nuclear ER and PR staining, it was regarded as positive. For MIB-1,Monoclonal Mouse Anti-Human Ki-67 Antigen, clone M 7240, (manufactured by DAKO) Denmark was used. Technical negative control from a lymph node with follicular lymphoid hyperplasia known to be immunoreactive for Ki-67 was used for MIB1.

The stained slides were examined by two pathologists and tumors were classified into subtypes according to the dominant growth pattern (roughly 50% of a specimen on microscopic evaluation) on hematoxylin and eosin sections. Their initial grade was recorded according to the WHO classification of CNS tumors 2021l.[2]

Immunohistochemical evaluation for the expression of was done on all grade 2 and grade 3 meningiomas and 30 cases of grade 1 meningiomas which were selected randomly. Thus, immunohistochemistry was done on a total of 76 cases which included 30 cases of grade 1 meningioma, 34 cases of grade 2 meningioma and 11 cases of grade 3. The MIB-1 LI was determined by a semi-quantitative scoring scale graded as follows: (0, absent; 1, weak; 2,

moderate; and 3, strong) and the percentage of positive tumour cells (0, indicating the absence of positive nuclei; 1, the presence of a few positive tumour nuclei totaling less than 10% of the section; 2, an estimated 10–50% positive nuclei; 3, 51–80% positive tumour nuclei; and 4, > 80% positive tumour nuclei). An immunoreactive score (IRS), which ranges from 0 to 12, was determined for each tumour in accordance with recommendations for breast cancer and meningioma tissue. The IRS was computed by multiplying the staining intensity by the indicator for positive tumour cells. Cancers with an IRS of 2 or above were deemed to be receptor-positive as described by Roser et al.[22]

Data were analysed using IBM SPSS ver. 27 software, and values were measured as median, mean and standard deviation (SD) according to the considered variables. Chi-square test was used to assess the association of gender, grade, and histological subtype of meningioma. A difference was considered statistically significant if the p-value was <0.05.

Results

A total of 276 patients were included in our study. The mean age of the study population was 49.68±12.85 years. Most of our patients were in 5th and 6th decade of life with age range of 5- 73 years. Only 5 (1.81%) patients belonged to the paediatric age group and were under the age of 18 years. 179 patient were females (64.86%) and 97 were males (35.14%) all of Kashmiri lineage and descent, with a female:male ratio of 1.8:1. Meningothelial meningioma was most the common histological type (38.8%) followed by transitional (19.6%) as shown in Figure 1.

Figure 1: Histological spectrum of meningiomas.

WHO Grade 1 meningioma was seen in 231(83.7%) patients, Grade 2 in 34 (12.3%) patients and Grade 3 in 11(4.0%)patients. When grade of tumor was compared to the gender it was seen that grade 2 and 3 meningiomas were more common in males as compared to females.

Immunohistochemical evaluation was done on 30 cases of grade 1 meningioma, 34 cases of grade 2 meningioma and 11 cases of grade 3 meningioma for the expression of estrogen receptor, progesterone receptor and MIB-1 LI. As the grade of meningiomas increased the percentage positivity for estrogen and progesterone receptor decreased significantly [Figures 2 and 3].

Figure 2: Progesterone receptor (PR) expression in GRADE I(A) Vs GRADE III(B) MENINGIOMA (IHC;40X).

Figure 3: Mean MIB-1 Vs PR status of cases.

MIB-1 labelling index for the sample studied ranged between 0 to 35%. The difference of MIB-1 labelling index with respect to the grade of tumor was statistically significant. While correlating the PR expression with the MIB-1 LI, it was observed that mean MIB-1 LI was higher in PR negative cases (7.21%) as compared to the PR positive cases (4.25%), hence showing an inverse correlation [Figure 4]. When the expression of MIB-1 LI was seen with respect to the gender, it was observed that the mean MIB-1 LI was higher in males (7.16%) as compared to the females(4.5%).

Figure 4: MIB LI OF GRADE II (A) VS GRADE III(B) MENINGIOMA (IHC;40X).

In our study population, 12 cases of recurrent meningiomas were seen (4.4%) with 7 cases being males and 5 cases being females. The mean age of recurrence was 49±13.5 years with ages ranging between 24 and 65 years. 50% of the cases presented in the young age group (<40 years) and in the elderly age group (> 65years). Out of the 12 recurrent cases, only 3 expressed progesterone receptors and one case was estrogen receptor-positive as shown in [Table 1].

Table 1: WHO GRADE OF MENINGIOMAS VS IHC STATUS (in percentage).

WHO GRADE	MALE	FEMALE	ESTROGEN RECEPTOR	PROGESTERONE RECEPTOR	MIB-LI (Median)
1	71	160	26	70	2.1
2	22	12	5.8	20	6.3

3	6	5	0	18	13.4

Among the recurrent cases it was seen that grade 2 tumors did not change their grade on recurrence. However, five out of eight grade 1 tumors showed an increase in grade from Grade 1 to Grade 2 upon recurrence. The mean time taken for recurrence to develop was 8.25 years ranging from 4 months to 32 years. The median MIB-1 LI of recurrent cases was 16.7. It was significantly higher as compared with non-recurrent cases.

Discussion

Out of a total of 276 cases, 64.86% were females. Similar results were seen by Shayanfar et al[23] and Nuaimy et al.[24] Meningothelial meningioma was the most dominant subtype (37.7%) followed by transitional meningiomas (19.6%) .

Grade 1 tumors formed the majority of our cases (83.7%) followed by grade 2 (12.3%) and grade 3 tumors (4%). Our results were in concordance with most studies in the literature. It was observed that 69.3% of grade 1 meningiomas occurred in females, hence showing a female preponderance of grade 1 meningiomas. However, grade 2 and grade 3 meningiomas were more common in males (64.7% of grade 2 and 54.5% of grade 3).

In our study the median MIB-1 LI for Grade 1 meningiomas was 2.1, for Grade 2 meningiomas was 6.3 and for grade 3 meningiomas was 13.4. In grade 1 meningiomas, MIB-1 LI acted as a control for comparison with high-grade meningiomas and was useful in instances that fell into the grey area (had some but not all characteristics of atypical meningioma).The occurrence of MIB-1 LI of >7% in a few benign WHO grade 1 meningiomas suggests that in some cases, focal areas of histological atypia may not be included in a biopsy.

Shayanfar et al, 2010[23] in their study recorded the mean MIB-1 LI as 2.98±2.27 in grade 1 tumors, 9.30±5.79 in grade 2 tumors and 34.00±5.47 in grade 3 tumors. Studies by Mukhopadyay et al[25] and Dutta et al[26] shows similar results.

Nuaimy et al, 2012[24] in his study documented atypical meningioma (grade 2) had Ki-67 LI in range between grade 1 and grade 3 meningiomas, with mean Ki-67LI ± SD of 5.4±2.8%. Kolles et al., reported that Ki-67 (MIB-1) LI is the most important criterion for distinguishing anaplastic meningiomas (WHO grade 3) (mean Ki-67 LI: 11%) from those of common type (WHO grade 1(mean Ki-67 LI: 0.7%).[27] Akyildiz et al[28] found a significant statistical relationship between Ki-67 LI and mitotic activity, necrosis, pattern loss, small cell change and brain invasion. Hence our results are in concordance with many studies in the literature.

No correlation between MIB-1 LI and histology of meningiomas was seen, although Ozen et al has reported the highest value in fibrous and lowest in secretory meningiomas.[29]

It was observed that the mean MIB-1 LI was higher in males (7.16%) as compared to females (4.5%). A significant relation was found between Ki-67 LI and the sex of the patients by Nuaimy et al[24] in their study.

Quantifying the hormonal status of the tumor may help to predict its biological behavior and provide options for further treatments. The higher incidence of meningiomas among women has led to the assumption that sex steroid hormones may influence the growth of meningiomas.[30]

Estrogen receptor expression was observed in 13.3% cases. It was seen that 26% of grade 1, 5.8% of grade 2 and none of the grade 3 meningiomas expressed the estrogen receptors ($p< 0.019$). No statistically significant correlation of estrogen expression was observed with histological subtype or gender in our study. Fakhrjou et al[31] in his study observed ER expression in 20% of cases and Dutta et al[30] observed 20.89% ER positive cases .Our results are hence in concordance with many studies in literature stating that the expression of estrogen receptors in meningiomas is either low or absent.

In our study 70% of grade I, 20% of grade 2 and 18% of grade 3 meningiomas expressed the progesterone receptors. Similar results were observed by Roser et al,[30] Nuaimy et al[24] and Dutta et al[26]in their studies.

Although not entirely unlikely, no association between PR status and age, gender, tumor location, and histology has been reported in the studies of the literature.[18,30] Statistical analysis of our data was done to confirm this and we found that no significant relation of PR expression was seen in reference to the above-mentioned variables. However, many studies in the literature point to higher expression of PR in female patients.[22,32] However these studies included a substantial number of atypical and malignant meningiomas. Therefore, the previously reported gender related difference might be the result of particular selection criteria, which produced a non- homogeneous patient population.

Mean MIB-1 LI was higher in PR negative cases (7.21%) as compared to the PR positive cases (4.25%), hence showing an inverse correlation. Similar results were seen by Nuaimy et al.[24]

We documented 12 cases of recurrent meningiomas (4.34%), with a male: female ratio of 1.4:1. however, no statistically significant relation could be derived due to less number of cases. The mean age of recurrence was 49± 13.5 years and the mean time period of recurrence was 8.25-yrs. Other studies also have reported higher recurrence rates for males than for females.[6,33] Recurring meningiomas cases of grade II made up 66.7%, grade I 25%, and grade III 8.3%, respectively. Grade II tumors did not change their grade on recurrence. However, some of the grade I meningiomas increased by one grade. Only 1 out of the 12 cases showed expression of estrogen receptors. 50% of grade 1, 16% of grade 2 and none out of grade 3 meningiomas (0%) were positive for expression of progesterone receptors. Our results are in concordance with most studies in the literature. PR negativity was strongly correlated with the recurrence of benign meningiomas[32], whereas the ER status was not significant. Roser et al[30] in their study concluded that Progesterone receptor (PR) status alone cannot be used to predict prognosis in meningiomas. However, in combination with the proliferative index, it can be a useful prognostic tool for benign meningiomas. Similar to most of the studies globaly,[34] the mean MIB-1 labeling index in recurrent cases was higher as compared to the mean MIB-1 labeling index of nonrecurrent cases. Hence our results, like other studies observed that higher MIB-1 LI correlates with an increased risk of recurrence, but the specific cut-off levels and counting techniques have varied considerably between studies.

This was a single-center study conducted at a tertiary care hospital in Srinagar, Jammu and Kashmir, India which caters to the local, mostly homogenous population comprising of a single race/ethnicity.

Conclusion

Both the grade and recurrence have a statistically significant positive connection with MIB-1 LI. For routine examination of meningiomas, especially those with borderline atypia, it is a helpful auxiliary approach. However, PR has a strong correlation with the histological grade and its expression is a positive prognostic indicator. When combined with MIB-LI, the Progesterone receptor (PR) status can shed more light on the behaviour of a meningioma, especially when subtotal resection, a high proliferative rate, or recurrence are present. This information can also be used as a prognostic tool to forecast the tumor's recurrence. Additionally, because meningiomas take a long time to recur, long-term follow-up investigations are needed to assess prognosis and recurrence.

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