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Original Research Article

Immunohistochemical Expression of Progesterone Receptors and Ki-67 in Meningioma

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Abstract

Introduction: Meningiomas are the most common primary benign tumors of the central nervous system (CNS) as well as intradural part of the spinal cord. The prevalence of expression of progesterone receptor (PR) among patients with meningioma has been reported to be determined by different clinicopathologic factors particularly tumor grade as it was established by the WHO. Ki-67 is a nuclear non histone protein. It is used as a marker of proliferative activity and as a prognostic indicator in many tumors like breast carcinomas, neuroendocrine tumors, prostate, brain, nephroblastomas and lung. ***Materials and Methods:*** This is a Prospective study conducted in the Department of Pathology at Dr. V.R.K. Women's Medical College Teaching Hospital & Research Centre. The study included histopathologically diagnosed cases of different histological variants of all intracranial and intraspinal meningiomas. A total number of 50 cases were studied over a period of 1 year. All intracranial and intraspinal meningiomas received at the Upgraded department of Pathology with adequate pre-operative, intra-operative and post-operative information, were included in the study. ***Results:*** The maximum number of cases were seen in the age group of 40-49 years (26.6%) followed by 50-59 years (23.3%). In the present study, out of 60 cases, 47 (78.3%) were females and the remaining 13 (21.6%) cases were males. Among the total 60 cases of Meningiomas, it was observed that intracranial location was more commonly involved comprising of 56 (93.3%) cases followed by Intraspinal location observed in 04 (6.6%) cases. Overall including the both grades total 51 cases out of 60 i.e. 85% were positive for PR, and 9 cases (including both the grades) i.e. 15% were negative for PR. Most of the grade I meningiomas (50 out of 56 cases i.e. 89.2% of grade I tumors) were positive for PR and few (6 out of 56 i.e. 10.7% of grade I tumors) were negative. ***Conclusion:*** Present study concluded that meningiomas will express PR. And this expression of PR has a significant inverse relationship with Ki- 67 i.e. as the Ki-67 expression denotes grade of meningioma, with increasing grade PR expression is reduced. So, Immuno histochemical staining with Ki-67 and PR antibody will help in deciding the grade of meningioma and helps to select the cases for which hormonal therapy can be employed.

Keywords: Progesterone Receptors, Ki-67, Meningioma, Immunohistochemical Expression.

INTRODUCTION

Meningiomas are the most common primary benign tumors of the central nervous system (CNS) as well as intradural part of the spinal cord. These are slow growing tumors; however, they may recur and cause significant morbidity and mortality [1]. According to the World Health Organization (WHO) report of 2007, meningiomas account for approximately 20% and 25% of all primary CNS and spinal cord tumors, respectively. Furthermore, the report revealed that approximately 30% of the diagnoses are usually established during autopsy.

The Central Brain Tumor report, which was produced in the United States among patients with meningiomas between 2004 and 2008, revealed that the age-adjusted incidence rate of meningioma was 3.76 per 100,000 person-years for men and 8.44 per 100,000 person-years for women [3]. In the United Kingdom, the epidemiology of meningiomas has remained constant for over 12 years from 1996 to 2008 where women have been reported to have a 2-fold increased risk of developing meningioma compared with men [4].

The prevalence of expression of progesterone receptor (PR) among patients with meningioma has been reported to be determined by different

clinicopathologic factors particularly tumor grade as it was established by the WHO [5]. One study reported that the expression of PR for grades I, II, and III was 96.8%, 20%, and 0%, respectively. Another study that was performed in German reported that only WHO grade I meningiomas were PR positive and all cases with WHO grades II and III were negative [6].

Other studies have shown that meningiomas that are positive for PRs usually have better prognosis and they have very limited chances of recurrence [7]. Because tumor biology has been reported to be influenced by genetical composition, which in turn is usually determined by the race of the individuals and also their geographical location [8].

Ki-67 is a nuclear non histone protein, with a chemical structure of and molecular weight ranging from 345 to 395 kDa. It is encoded by gene which is located on chromosome 10q26. Ki-67 is used as a marker of proliferative activity and as a prognostic indicator in many tumors like breast carcinomas, neuroendocrine tumors, prostate, brain, nephroblastomas and lung [9].

Ki-67 and MIB-1 monoclonal antibodies are directed against different epitopes of the same proliferation-related antigen. Ki-67 and MIB1 may be used on fixed sections. MIB-1 is used in clinical applications to determine the *Ki-67 labelling index*. One of its primary advantages over the original Ki-67 antibody (and the reason why it has essentially supplanted the original antibody for clinical use) is that it can be used on formalin-fixed paraffin-embedded sections, after heat-mediated antigen retrieval [10].

This was done for the purpose of addressing the knowledge gap that exists regarding the level of expression of PR and the way it may show association with the clinicopathological factors.

MATERIALS AND METHODS

This is a Prospective study conducted in the Department of Pathology at Dr. V.R.K. Women's Medical College Teaching Hospital & Research Centre. The study included histopathologically diagnosed cases of different histological variants of all intracranial and intraspinal meningiomas. A total number of 50 cases were studied over a period of 1 year.

Inclusion criteria: All intracranial and intraspinal meningiomas received at the Upgraded department of Pathology with adequate pre-operative, intra-operative and post-operative information, were included in the study.

Exclusion criteria: Those specimens with inadequate tissue and /or clinical data were excluded.

Haematoxylin-eosin stained slides of all histopathologically diagnosed case of meningiomas of different variants were taken. Depending upon Presence or absence of Brain invasion and by various histological criteria (defined by WHO), these cases were graded as grade 1 and grade 2. The most representative block for all 50 cases was then selected for Immuno histochemical analysis by PR antibody and MIB-1 antibody.

Additional immunohistochemistry with Glial fibrillary acidic protein (GFAP), and special stain with PAS was performed in required cases, to contribute in the histopathological diagnosis of the cases.

Appropriate positive and negative controls were used for each antibody. Breast tumours which are positive for PR were taken as control for the assessment of PR. For Ki-67, sections from lymph node showing reactive hyperplasia were taken as positive control. The primary antibody was omitted in the negative controls.

Statistical Analysis:

The statistical analysis was done for all the data using Chi-square test and Fisher exact test. The results were considered statistically significant if the P value was <0.05.

RESULTS

The present study comprises of 60 cases of Meningiomas. All the cases which were diagnosed histopathologically, taken and Immuno Histochemistry was performed with PR and Ki-67 on all the cases.

Table 1: Age distribution pattern in Meningiomas

Age group (years)	Number of cases	Percentage (%)
10-19	02	3.3%
20-29	09	15%
30-39	11	18.3%
40-49	16	26.6%
50-59	14	23.3%
60-69	07	11.6%
70-79	01	1.6%
Total	60	100%

The age of the patients ranged from 10-89 years including 2 children below the age of 18 years. The maximum number of cases were seen in the age group of 40-49 years (26.6%) followed by 50-59 years (23.3%). The least number of cases were seen in patients of age group 70-89 years (1.6% in each decade) in table 1.

Table 2: Gender distribution pattern in Meningiomas

Gender	Number of cases	Percentage
Female	47	78.4%
Male	13	21.6%
Total	**50**	**100%**

In the present study, out of 60 cases, 47 (78.3%) were females and the remaining 13 (21.6%) cases were males. The male to female ratio was 1:4 in table 2.

Table 3: Distribution of the cases according to the Location

Location	Number of cases	Percentage (%)
Intracranial	56	93.3%
Intraspinal	04	6.6%
Total	**60**	**100%**

Among the total 60 cases of Meningiomas, it was observed that intracranial location was more commonly involved comprising of 56 (93.3%) cases followed by Intraspinal location observed in 04 (6.6%) cases in table 3.

Table 4: PR expression in GRADE I meningiomas (56 cases)

Histological variants	Positive for PR	Negative for PR	TOTAL
Meningothelial	13	00	13
Fibroblastic	00	01	01
Transitional	33	00	33
Psammomatous	00	04	04
Angiomatous	04	00	04
Microcystic	00	01	01
TOTAL	**50**	**06**	**56**

Overall including the both grades total 51 cases out of 60 i.e. 85% were positive for PR, and 9 cases (including both the grades) i.e. 15% were negative for PR. Most of the grade I meningiomas (50 out of 56 cases i.e. 89.2% of grade I tumors) were positive for PR and few (6 out of 56 i.e. 10.7% of grade I tumors) were negative in table 4 and 5.

Table 5: PR expression in GRADE II meningiomas (6 cases)

Histological variants	Positive for PR	Negative for PR	TOTAL
Clear cell	00	01	01
Atypical	01	02	03
	01	**03**	**04**

Most of the Grade II meningiomas (3 out of 4 cases i.e. 75%) were **negative** and only one case (1 out of 4 cases.i.e.25%) was positive in table 5.

Table 6: Ki-67 LI in different histological variants

Grade	Histological Variant	No. of Cases	Ki-67 Li Range	Median Ki-67 Li
GRADE I	Meningothelial	13	0.6-6.5%	3%
	Fibroblastic	01	1%	1%
	Transitional	33	0.5-1.5%	1%
	Psammomatous	04	0.5-1%	0.6%
	Angiomatous	04	1-2%	1.5%
	Microcystic	01	2%	2%
GRADE II	Clear cell	01	2%	2%
	Atypical	03	3-7%	5%

From the above table, high Ki-67 labelling index was observed in atypical variant and low Ki-67 Labelling Index was observed in Psammomatous and Transitional variants.

Table 7: Distribution of cases in relation to the Ki-67 LI and histological grade

Histological grade	No. of cases with median Ki-67 LI <4%	No. of cases with median Ki-67 LI >4%	Total
Grade I	55	01	56
Grade II	02	02	04
Total	**57**	**03**	**60**

Table 8: Distribution of cases in relation to the Median Ki-67 LI and PR expression status.

PR status	Ki-67 LI < 4%	Ki-67 LI > 4%	Total
PR Positive	50	01	51
PR Negative	06	03	09
Total	**56**	**04**	**60**

DISCUSSION

Reporting on the prognostic role of the PR among patients with meningiomas is of utmost importance due to the fact that it may help invention of PR inhibitors that can be of therapeutic benefit to the patients. Furthermore, the discovery of such drugs may be used for personalized medicine that in turn helps to prevent unnecessary exposure to chemotoxicity and also it reduces the possibility of incurring unnecessary expenses [11].

Prevalence of Expression of Progesterone Receptor for the FFPE Tissue Blocks of the Cases Included in the Study PRs have been found to be highly expressed in meningiomas. This was also reflected in the present study in which over 50% of the cases were PR positive. However, previous studies performed in Caucasians and Africans have reported higher prevalence of PR expression than the prevalence reported in our study. For example, the studies that were performed in Iran, the United States, Nigeria, and India reported the prevalence of PR expression in FFPE tissue blocks of patients with meningiomas of 96%, 82.9%, 87.5%, and 65%, respectively [12].

Lower prevalence of PR in meningiomas than the one observed in the present study has also been reported elsewhere. The studies that were performed in the United Kingdom, North Korea, and Brazil reported the prevalence of PR expression of 48%, 31.9%, and 53.4%, respectively [13]. The difference in expression of PRs across the studies may have various reasons including the difference in the methodology used, tumor biology, and genetical constitution of the individual included in the different studies. Studies have shown that delayed fixation and long-term storage of the FFPE tissue blocks may render the FFPE tissue blocks negative for IHC staining [14].

Therefore, timely fixation of the specimens and optimal storage time of the FFPE tissue blocks help to increase the level of IHC antibodies including PRs. Association Between Expression of Progesterone Receptor and Clinicopathological Characteristics The expression of PRs in meningiomas has been found to be associated with different prognostic factors such as age of the patients, sex, tumor grade, and tumor location among many others [15]. Regarding the association of sex with PR expression in our study, we found that over half of the cases showing PR expression were females. However, there was no association between PR expression and sex. Lack of association between the expression of PR and sex among patients with meningiomas in spite of female preponderance has also been reported in other studies [16].

The association of age with expression of the PRs in meningiomas seems to be contradicting. Some studies have reported a positive association between age and expression of the PR, whereas other studies did not find any association between the 2 variables. Some studies have reported that there is a high trend of expression of PR among older patients compared with younger patients with meningiomas [17]. We found a positive association between age and expression of PR (P ¼ 0.043), and the expression of the biomarker was increasing with the increase in the age of the patients. This is similar to the finding of the study performed by Roser et al, who reported that patients who were histopathological subtypes [18].

A study conducted in Egypt by Shayanfar et al showed that 57% of meningiomas were mixed with psammoma bodies and a few of them could express the PRs similar to the finding in the current study, in which 25% of the meningiomas had psammoma bodies and showed either negative or weak intranuclear staining for the PRs. This has been explained by the fact that psammomatous meningiomas are more likely not to express the PRs because of being calcified by virtual of the presence of psammoma bodies that require decalcification so as to unmask the epitopes for the PR antibody to stain easily [19].

CONCLUSION

Present study concluded that meningiomas will express PR. And this expression of PR has a significant inverse relationship with Ki- 67 i.e. as the Ki-67 expression denotes grade of meningioma, with increasing grade PR expression is reduced. So, Immuno histochemical staining with Ki-67 and PR antibody will help in deciding the grade of meningioma and helps to

select the cases for which hormonal therapy can be employed. And also helps in predicting the tumor behaviour.

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