Original Article

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Hormone Receptor Status and KI67 Proliferation Index in Meningiomas

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ABSTRACT

Background: Meningiomas are the most common extra-axial tumours of central nervous system arising from arachnoidal cap cells. The biological behaviour of these tumours is unpredictable because of the tendency of these tumours to recur irrespective of the grade. However, WHO grading is the most useful morphological predictor of recurrence. Additional prognostic parameters like Ki67 proliferation index and progesterone receptor status are useful in predicting the risk of recurrence. This study was undertaken to evaluate the spectrum of Ki67 proliferation index in various grades of meningiomas and to correlate these findings with the hormone receptor status.

Methods: In this study 225 cases of meningiomas, over 6 yrs period, were studied which included grade 1 and grade 2 meningiomas. The relation between Grade, Ki67 proliferation index and progesterone receptor status was studied.

Result: We found a significant positive correlation between grade and Ki67 proliferation index at 0.01 level and significant negative correlation between Grade and progesterone receptor status at 0.05 level. There was also significant negative correlation between progesterone receptor status and Ki67 proliferation index in cases with progesterone receptor staining score of 6 to 12. Many of the grade 1 meningiomas also showed a higher Ki67 proliferation index

Conclusion: In this study we conclude that, PR and Ki67 Proliferation index are useful supplements of routine histopathological assessment of meningiomas and can be used as prognostic indicators regarding behavior and response to treatment.

Keywords: *Hormone Receptors, Progesterone Receptor, Ki67 Proliferation Index, Atypical Meningioma*

Introduction

Meningiomas are the most common central nervous system (CNS) tumours[1] and the most common of the extra-axial tumors which are derived from arachnoidal cap cells. They occur with a frequency of 19% at intracranial and 25% at spinal localisations.[1] Most of them are benign, slow-growing neoplasms. According to 2016 WHO classification of CNS tumours, the various subtypes are broadly categorized into 3 grades, Grade 1, Grade 2 and Grade 3 depending on the morphology and biological behavior of these subtypes. Some histological variants of meningioma are more likely to recur. However, overall, WHO grade is the most useful morphological predictor of recurrence. Additional prognostic parameters include Ki67 proliferation index (Ki67 PI) and hormone receptor status. The presence of hormonal receptors i. e. Estrogen and Progesterone receptors (ER and PR) would help for hormonal manipulation of meningiomas in patients with recurrence, incomplete surgical resection and in inaccessible tumors. This study was undertaken to evaluate the spectrum of Ki67 PI in various grades of meningiomas and to correlate these findings with the hormone receptor status.

Materials and Methods

This is a prospective study which included 225 cases of meningiomas diagnosed during the period from 2013 to 2018. Clinical details were obtained from hospital records and requisition forms received in histopathology department. The specimens were routinely processed and 3 to 4 micron thick sections were made from formalin-fixed paraffin embedded blocks. These sections were stained with Haematoxylin and Eosin. All the meningiomas were histologically graded according to 2016 WHO grading system. Ki67 PI and ER, PR expression were studied by immunohistochemistry using peroxidase method. For ER & PR, Rabbit monoclonal antibody clone EP1 and EP2 from Pathnsitu were used. For Ki 67 proliferation index, Mouse monoclonal antibody clone GM001 from Pathnsitu was used. The results of receptor status was interpreted by a semi-quantitative scoring scale as described by Roser et al.[1] Staining intensity was graded as 0- absent, 1-weak, 2-moderate, 3-strong. With respect to percentage of positive tumor cells, they were scored as presence of 0 staining, indicating absence; 1, few positive tumor nuclei <10% in the entire section; 2, 10-50% positive nuclei; 3, 51-80% positive tumor nuclei; and 4, >80% positive

nuclei. As recommended for breast cancer[1] and verified with meningioma tissue,[2] an immunoreactive score (IRS) was calculated. Tumors with IRS range of 2 or more were considered receptor positive. For assessment of Ki67 PI, areas with the highest density of Ki67 immunostained nuclei were selected, and the Ki67 PI was expressed as a percentage of positively stained cells out of 1000 tumor cells counted. The results were compiled and assessed.

Result

We studied 225 cases of meningioma over a period of 6 years. F: M ratio was 1.6:1. Age group ranged from 13yrs to 80yrs. Majority (32%) were in the age group of 41-50 yrs age. There were 195 (87%) grade 1 and 30 (13%) grade 2 cases. Grade 1 cases included meningothelial, fibroblastic, transitional, psammomatous, secretory, angiomatous and microcystic meningiomas. Grade 2 cases included 27 cases of atypical meningiomas, 2 cases of clear cell and 1 case of chordoid meningiomas. There was no grade 3 meningiomas encountered during the study period. Meningothelial meningioma was the most common histological subtype (44%). PR positivity was more common in meningothelial subtype (Table 1). Mean Ki67 PI was 3.3% in grade 1 and 10.4% in grade 2 meningiomas i. e. grade 2 meningiomas showed significantly higher mean Ki 67 PI compared to grade 1 cases (Table 2). There was significant positive correlation between grade and Ki67 PI at 0.01 level using Pearson correlation tests (r value = 0.5). All the 225 cases were ER negative. PR was positive in 167(74%) cases. Percentage of PR positive cases in females was 75.2% and in males it was 72.7% (Table 2). There was no statistically significant correlation between age, sex and PR status or grade. Among the grade 1 cases, 75.4% cases were PR positive and among grade 2, 66.6% cases were PR positive. There was significant negative correlation between grade and PR status at 0.05 level using pearson correlation tests (r value = -0.2) (Table 2). There was weak negative correlation between Ki67 PI and PR status (r value= -0.1). We observed a significant negative correlation between the cases with higher PR score (6-12) and Ki67 PI at 0.05 level using pearson correlation tests (r value = -0.2) (Table 3). 12 cases of recurrent meningiomas were encountered which included 9 cases of grade1 and 3 cases of grade 2 meningiomas. Mean Ki67 PI in recurrent grade 1 meningiomas was 5.0%. Mean Ki67 PI in nonrecurrent grade 1 cases was 3.2%. We observed a significant negative correlation between PR score and Ki67 PI in recurrent meningiomas at 0.05 level using pearson correlation tests (r value = -0.4). There was no correlation between site and Ki67 PI or PR status.

Table 1: PR positivity in various histological types of meningiomas.

Histological type	No of cases	No PR positive cases
Meningothelial	100	79
Fibroblastic	18	11
Transitional	46	33
Psammomatous	9	7
Angiomatous	17	13
Secretory	4	3
Microcystic	1	1
Clear cell	2	0
Chordoid	1	0
Atypical	27	20

Table 2: PR positivity and mean Ki67 PI in meningiomas.

	PR positive	PR negative	Percentage of PR positive cases	Mean Ki67 PI
Males	64	24	72.7%	4.7%
Females	103	34	75.2%	3.9%
Grade 1	147	48	75.4%	3.3%
Grade 2	20	10	66.6%	10.4%

Table 3: Correlation between PR score and Ki67 PI.

PR score	PR positive cases	Mean IRS	Mean Ki67 PI
2-5	60	3	3.8%
6-12	107	9	4.2%
Total	**167**		

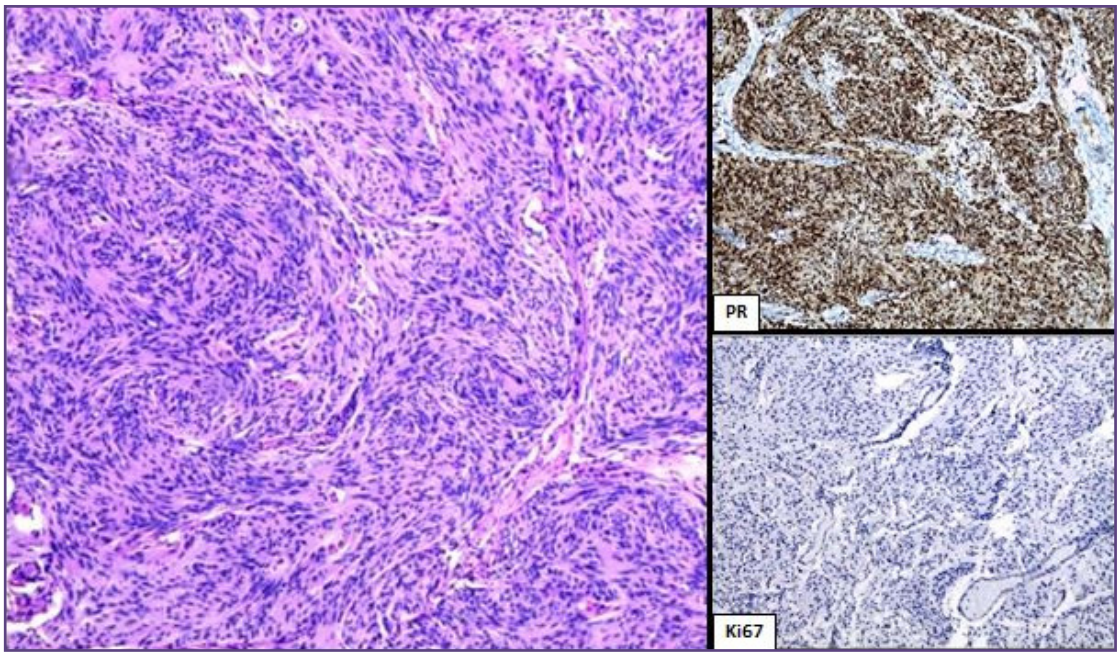

Fig. 1: Grade 1 meningioma with high PR score and low Ki67 PI (H & E stain, 100X).

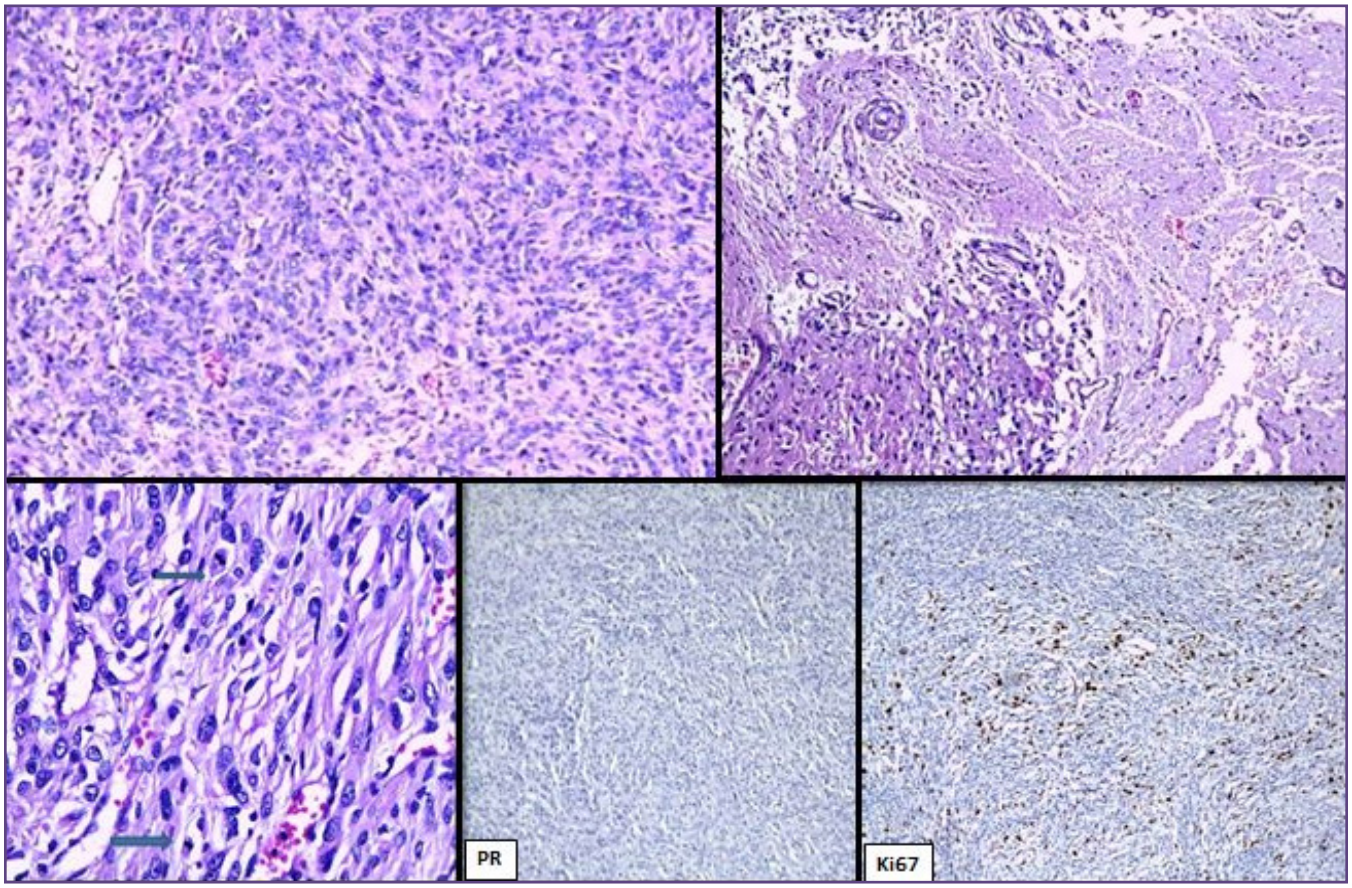

Fig. 2: Grade 2 meningioma with negative PR and high Ki67 PI (arrows – mitoses, asterisk– brain invasion) (H & E stain, 100X, 400X).

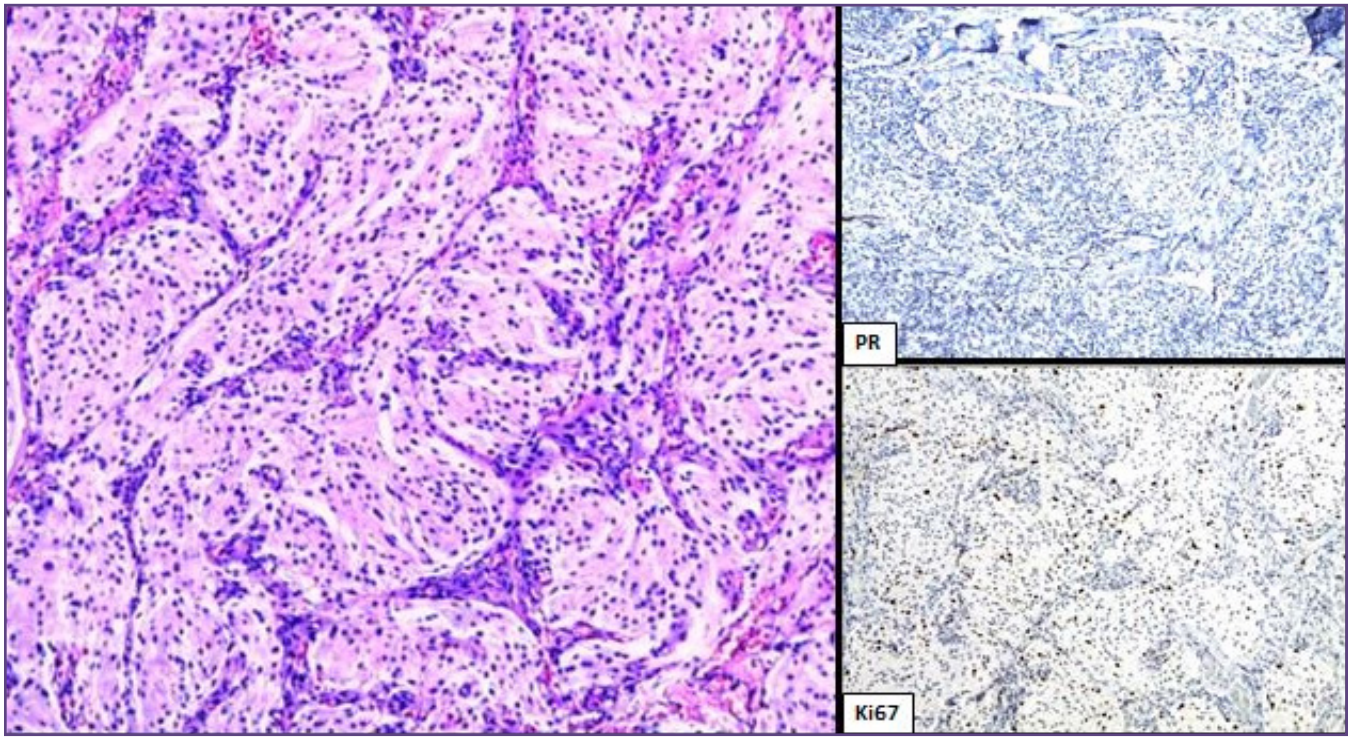

Fig. 3: Grade 1 meningioma with negative PR and high Ki67 PI (H & E stain, 100X).

Discussion

Hormone receptors in meningiomas were first described by Donnel et al in 1979 using receptor binding assays.[3,4] Since then, many authors have studied the relation between sex hormone receptors and meningiomas.[5-11] It is assumed that sex steroid hormones may influence the growth of meningiomas because of higher incidence of meningiomas among women, their behaviour during pregnancy, and the reported epidemiological link between meningiomas and breast carcinomas.[1] Since the meningiomas show variable growth potential, and even the WHO microscopic morphological classification frequently fails to predict their clinical behaviour, quantifying the hormonal status of the tumor may help to predict its biological behaviour and provide options for further treatments. It is generally agreed that most meningiomas express PR but are devoid of ER. As with many other tumors, Ki67 PI provides additional information regarding the proliferation index.[2,10]

In this study, we studied the hormone receptor status and Ki67 PI in meningomas over a period of 6 years which included 225 cases. Majority of the patients were in the age group of 41-50 yrs and meningothelial meningioma was the most common subtype. F: M ratio was 1.6:1. All the cases were ER negative. PR was positive in 74% of cases. Some authors demonstrated the presence of the PR positive meningiomas using different methods such as a hormone binding assay or Enzyme immunoassay, or immunohistochemistry.[12] Khalid[13] reported that all cases were positive for the PR. Hsu et al[14], reported that nuclear staining for the PR was found in 83%, and Perrot-Applanat et al[10], noted that, using immunohistochemical method, the PR was found to be present in 72% of meningiomas.

We found a higher incidence of meningiomas in females (F:M ratio, 1.6:1) but there was no statististically significant difference in PR status, between males and females. Percentage of PR positive cases in females was 75.2% and in males it was 72.7%. There was no statistically significant difference between PR status and age, sex and histological type. This was in accordance with other studies where the authors have reported that the presence of the PR in meningiomas did not correlate with the age or sex of the patients.[2,10,13-20] Brandis et al[2] noted that 60% of the female and 62.5% of the male patients had the PR expression.

There are studies where they found a clear relationship between the presence of the PR and the histological type of the tumor. [10,15,21,22] Horsfall et al[21], reported an increased presence of the PR in the meningothelial type. Markwalder et al[15] also noted that the PR expression was associated with certain histological features, with a predominance of PR positivity in the meningothelial subtype. Perrot-Applanat et al[10] observed that the PR immunostaining

was found more frequently in the meningothelial and in the transitional than in the fibroblastic histological types. In the present study, we found that PR positivity was more common in meningothelial subtype (47%). Carroll et al[23] and Schrell et al[24] did not find any correlation between histological type and PR status.

In our study PR positivity was higher in grade 1 meningiomas compared to grade 2 meningiomas. Among the grade 1 cases 75.4% cases were PR positive and among grade 2, 66.6% cases were PR positive. There was significant negative correlation between grade and PR status (Fig 1,2). This is similar to study done by Roser et al[1] who confirmed the presence of significantly higher PR values in benign meningiomas compared with WHO grade II or III tumors. Cahill et al[3] and Brandis et al[2] reported that malignant meningiomas are devoid of PR and ER. Many authors demonstrated a close correlation between the PR status and the tumor differentiation, and noted that most non-benign histological subtypes of meningiomas were negative for the PR. [2,9,14,22,25] Hsu et al[14] noted an inverse correlation between the tumor grade and the PR staining score, and concluded that an absence of the PR was significant factor for shorter disease-free intervals. Brandis et al[2] also found that non-benign variants more frequently showed an absence of the PR. They concluded that the PR status in meningiomas was related to the tumor differentiation and might be of prognostic value with regard to biological behavior and clinical outcome. Similarly, Lesch et al[26] and Olson[25] found significantly lower PR levels in atypical and malignant meningiomas. But, other studies[16,23,27] showed no relationship between the tumor grade and the presence of the PR.

In our study Ki67 PI of all the cases were analyzed. Mean Ki67 PI was 3.5% in grade 1 and 10.4% in grade 2 meningiomas i. e. grade 2 meningiomas showed significantly higher mean Ki 67 PI compared to grade 1 cases (Fig1,2). There was significant positive correlation between grade and Ki67 PI. Roser et al[1] proposed that PR status affected survival only in combination with the proliferation marker ki-67.

In our study the mean Ki67 PI in PR positive and PR negative meningiomas was 4.1% and 4.5% respectively. We observed a significant negative correlation between the cases with higher PR score (6-12) and Ki67 PI at 0.05 level using pearson correlation tests (r value = -0.2). There was decrease in PR score as Ki 67 PI increased (Fig 3). This is in accordance with Nagashima et al[9], reported that the Ki-67 staining index of the PR positive meningiomas were significantly lower than that of the PR negative meningiomas. They insisted that the PR status might be closely related to the growth potentials of the meningiomas. Markwalder et al[11] and Perrot-Applanat et al[10] noted that there was no significant correlation between the PR status and the Ki-67 staining index.

Maiuri et al[28] showed that proliferative index and PR status have a strong predictive value. Whittle et al[29] showed that PR negative meningiomas were biologically more aggressive than PR positive ones. Wolfsberger et al[30] found that the highest PR index is observed in patients under the age of 50 years with WHO grade I meningiomas of the meningothelial subtype and low cell proliferation index.

In our study we encountered 9 cases of recurrent grade 1 meningiomas. Mean Ki 67 PI in recurrent grade 1 meningiomas higher (5.0%) compared to nonrecurrent grade 1 cases (3.2%). Yamasaki et al[31] reported that Ki67 PI of recurrent tumors were higher. There was significant negative correlation between Ki67 PI and PR score of recurrent cases at 0.05 level (r value = -0.4). All these patients presented to our hospital during the recurrence, there were no details available regarding previous excision and histology.

Walter et al[32] has shown that preoperative administration of medroxy progesterone in patients with meningiomas that have positive PR receptors would show better clinical response when compared to patients who had tumor cells that were without PR receptors. Vissa shanthi et al[4] found that the tumors with high proliferative activity showed low PR expression. They proposed that though surgery is the treatment for the meningiomas, in some cases where tumor is not accessible to surgery or in elderly patients or in malignant tumors where complete removal is not possible due to invasion into the adjacent structures, antiprogesterone agents can be used in addition to radiotherapy. Taghipour et al[33] reported that positive progesterone receptor status is associated with better prognosis. Wahab et al[34] reported that the tumors with positive progesterone receptors had less recurrence rate. However studies done by Roser et al[1] suggested that only PR status cannot predict the prognosis in these tumors. The proliferative index should be used in combination with PR status to predict the prognosis of meningiomas. In the study conducted by Vibha Dutta et al[35], they suggested that PR status is an important prognostic factor in meningioma, more so in combination with proliferative index.

In our study all the cases were followed up with clinical and radiological assessment to look for recurrence. The average follow up period ranged from 6 months to 5 years. Accept 9 cases of recurrent meningiomas which presented

to us during recurrence, no other cases presented with recurrence during the study period.

Conclusion

Meningiomas are the tumours showing variable growth potential. Since benign(grade1) meningiomas may also show recurrence, the recurrence cannot be predicted by histomorphological features alone. Cell proliferation indices like Ki67 PI along with PR status can be used as a guide in grading of meningioma and therefore in prediction the recurrence potential of them. Our study suggests that PR status, in combination with Ki67 PI, is an important prognostic factor in meningioma. Meningiomas with higher proliferation index and negative PR have higher recurrence potential. But the PR status alone cannot be used to predict behaviour in meningiomas and should not influence therapeutic strategies. Studies have shown that use of antiprogesterone agents might result in better clinical response. But these studies are yet to be verified. In this study we propose that, PR and Ki67 PI immunohistochemical staining are useful supplements of routine histopathological assessment of meningiomas and can be used as prognostic indicators regarding behaviour and response to treatment.

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