Progesterone and Estrogen Receptors in Meningiomas – A Clinicopathological Analysis

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Abstract: *Background*: Meningiomas are common tumors of the Central Nervous System. Recurrence in meningiomas has been proven to be associated with factors like extent of resection and grade of tumor. Decrease in progesterone receptor expression has been linked to increased rate of recurrence. We undertook this study to know about progesterone and estrogen receptor expression in meningiomas and its association with different clinicopathological variables as data is lacking in the Indian population.

Materials and Methods: Meningiomas operated in a tertiary referral centre of North Kerala, India in 2 years were taken into the study. The tumors were graded and immunohistochemistry was performed using antibodies to Estrogen and progesterone receptors (ER&PR) and Ki-67. The expression of PR and ER was correlated with clinicopathologic variables. The patients were followed up for 2 years.

Results: Grade I and grade II tumors constituted 85.3% and 14.7% respectively of the total number of meningioma cases. There were no grade III tumors in the series. The average PR positivity in grade I tumors (60.77%) was higher than in grade II tumors (46.88%). There was no gender related difference in PR staining. ER positivity was found only in a few cases.

Conclusion: PR deterioration was associated with increased cell turnover. Meningiomas occurring in this study population are similar in clinicopathological parameters to those tumors occurring in other parts of the country but different in some aspects like grade from tumors occurring in other parts of the world. Strict follow up of a larger cohort of patients for a longer time period will be required to draw conclusions about prognosis in this population.

Keywords: Meningioma, Immunohistochemistry, Progesterone receptor, estrogen receptor, MIB-1.

INTRODUCTION

Meningiomas are neoplasms arising from the arachnoid cap cells. They are the most common intracranial tumors in adults [1]. The main prognostic factors in meningiomas are the extent of resection and histologic grade [1]. The resection in turn depends on extent of invasion, attachment to vital structures and the expertise of the surgeon. The World Health Organization (WHO) divides meningiomas into 3 grades of increasing malignancy. Grade I includes nine variants and grades 2 & 3 include 3 variants each [1]. Large majority of meningiomas are benign (grade 1) and amenable to surgical resection. The recurrence rate in completely resected grade I tumors is about 20% at 10 years. Malignant behaviour in meningiomas manifests as local recurrences and spread along the craniospinal axis. The recurrence rate at 10 years for Grade II tumors is 50% and for grade III tumors is 66% [2]. Extracranial metastasis is an extremely rare phenomenon. MIB-1(Mindbomb homolog -1) labeling index has been a proven prognostic indicator along with the grade of the tumor. Steroid hormone receptor expression in meningiomas is a long known factor and it has been proposed that this has a role in tumorigenesis [3]. Progesterone agonists have been implicated in meningioma growth [4]. Anti progesterone therapy has been used in recurrent and untreatable tumors [5-8]. But studies regarding their expression and correlation with prognostic variables are scarce in our population.

AIMS AND OBJECTIVES

1) To evaluate the status of progesterone and estrogen receptors (PR & ER) and proliferation marker Ki67 in various grades of meningioma

2) To correlate these values with clinico-pathological parameters

3) To evaluate whether PR deterioration is associated with cell turnover

MATERIALS AND METHODS

All cases of meningiomas operated in 2 years were retrieved from the registers of the departments of Pathology and Neurosurgery of Govt. Medical College,

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Kozhikode. The clinical details were collected from the case records of the Neurosurgery department. Paraffin blocks were retrieved. Hematoxylin and Eosin (H&E) stained sections were reviewed in detail. Subtyping and grading were done according to WHO classification of CNS tumors [1]. The various histological features – cellularity, presence of whorls, psammoma bodies, pattern of growth (meningothelial, transitional, fibroblastic, psammomatous, angiomatous, microcystic, secretory and patternless), nuclear atypia, nucleoli, small cells, inflammatory cells, necrosis, mitoses/10 high power fields and brain invasion were noted. Immunohistochemistry was done on formalin fixed paraffin embedded sections for PR (Dako USA, prediluted), ER (Dako USA, prediluted) and Ki-67 (Dako USA) antigen incorporating appropriate positive and negative controls. Percentage of nuclei positive for ER, PR and Ki-67 (MIB-1 Labeling index) were calculated by counting at least 500 nuclei. Patients were called for review and follow-up was noted by clinical examination and radiology where indicated, at 24 months after surgery.

RESULTS

99 cases of meningiomas - 91 primary and 8 recurrent- were operated during two years. The details of previous surgery were available only in 2 of the recurrent tumors. We could retrieve the paraffin blocks of 68 cases including 4 recurrent cases and hence only 68 cases were included in this study. There were 58 grade I (85.3%), 10 grade II (14.7%) and no grade III tumors among these. There was only one grade III tumor in the study period, but the paraffin block of the same was not available for study. One of the grade II tumors was recurrence of a grade I meningioma with micronecrosis resected 6 years back; the rest were primary tumors. The age ranged from 12-75 years; mean of 48.5 years. The highest number of patients was in the 5th and 6th decades in both grades I&II tumors. There were 44 female patients (64.7%) and 24 male patients (35.3%). Male:Female ratio was 1:1.83. There was only a single pediatric patient (1.47%); a boy aged 12 years with a grade II tumor (Figure **1**). This was a large contrast enhancing lesion with midline shift and perilesional edema. A higher proportion of grade II tumors was found in males as 6 out of the 10 grade II tumors (60%) were in males. Ninety percent of tumors were intracranial and 10% were spinal. Common sites of tumor included convexity, falx, posterior fossa, spine and skull base. Among the spinal tumors, the most common location was the thoracic spine. There were 2 intraventricular tumors, one in the lateral and the other in the 3rd ventricle and there was one primary extradural tumor involving parietal bone.

Follow-up could be obtained in only 43 cases out of which the paraffin block was available for immunohistochemical analysis in 31 cases. Three out of the 43 patients who were followed up had recurrence at 2 years. As the number of tumors in the recurrent group was very low, the groups were not comparable.

In histopathological analysis, there were 12 meningothelial, 29 transitional, 8 fibroblastic, 8 psammomatous, one angiomatous and one tumor which had a combination of microcystic, angiomatous and secretory patterns. Transitional pattern was the

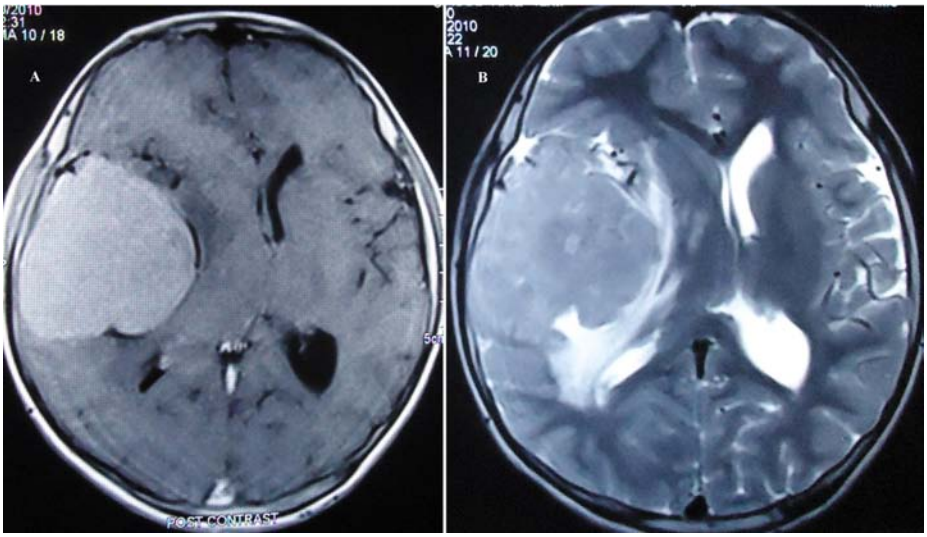

Figure 1: T1 weighted MR image of atypical meningioma after contrast showing a contrast-enhancing tumor with midline shift (**A**). T2 weighted image showing perilesional edema (**B**).

most common (Figure **2A**). Most of the tumors with angiomatous, microcystic and secretory morphology showed perilesional edema like higher grade lesions, as illustrated in Figure **3**. All of the grade II tumors had the morphology of atypical meningioma. There were no clear cell or chordoid tumors.

Average number of mitoses per 10 high power fields was 4.2 for grade II atypical meningiomas.

Brain invasion was seen histopathologically in 8 out of the 68 tumors (11.8%). Five of these tumors were grade I and the rest were grade II. The three tumors that had recurrence at follow up did not show brain invasion.

Immunohistochemistry for PR was positive in 65 cases (Figure **2B**). These included 55 out of the 58 grade I tumors and all 10 grade II tumors. PR was positive in 41 out of the 44 female patients and the average positivity was 57.83%. PR positivity was seen in tumors of all male patients and the average positivity was 60.83%. Therefore there was no gender related difference in PR staining. The average PR positivity in grade I tumors (60.77%) was higher than in grade II tumors (46.88%) though it ranged from 0 to 97%. Among the grade 2 tumors the lowest was 9%.

IHC for ER was significantly positive only in 4 grade I tumors. 25 tumors showed weak positivity in <10% of tumor cells (Figure **2C**).

MIB (MindBomb Homologue-1 labelling index was more for grade II tumors (Figure **3**). Mean MIB-1 LI was 1.25 for grade I and 6.9 for grade II tumors.

DISCUSSION

Various studies from different parts of the world have looked into the Progesterone and Estrogen receptor status and MIB-1 labelling in meningiomas and correlated it with different clinicopathologic

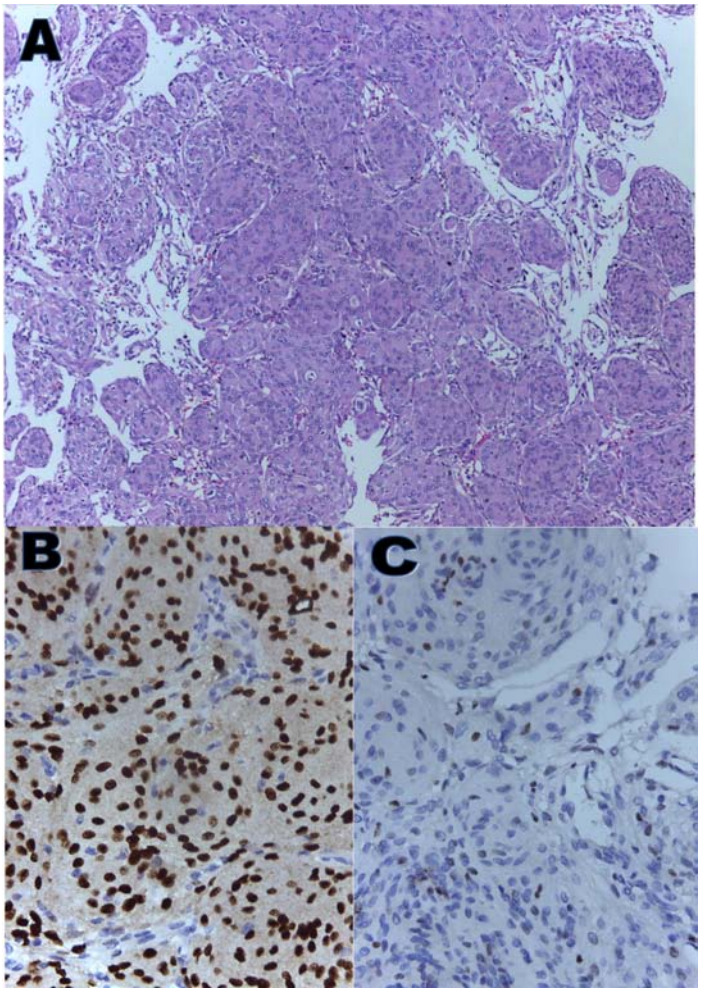

Figure 2: Transitional meningioma composed of whorls of tumor cells (**A**) (H&E X100). Strong PR positivity in most of the tumor cell nuclei (**B**) (PR X200). Weak ER positivity in a few tumor cell nuclei (**C**) (ER X200).

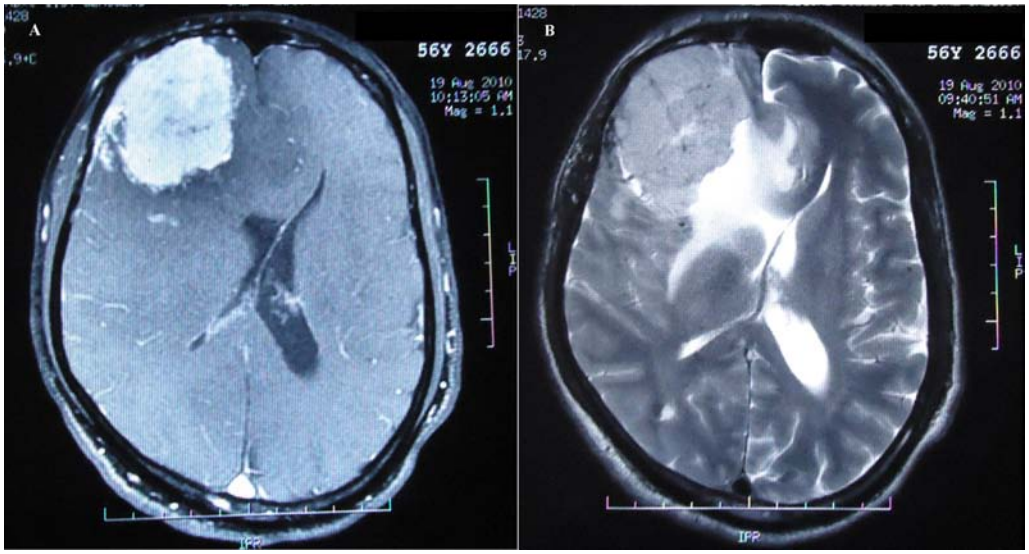

Figure 3: T1 weighted MR image of Angiomatous meningioma showing contrast enhancement and midline shift (**A**). T2 weighted image showing perilesional edema (**B**).

parameters especially the behavior of the tumors as regards their recurrence [2,9-12]. But the results have been different in different populations. So we undertook this study to know about clinicopathologic characteristics of meningiomas in the population of Kerala in which there is as yet scarce published literature regarding the same. The only other study was on atypical meningiomas but ER and PR status and MIB-1 labeling were not assessed [13].

The total number of tumors in the 2-year period was comparable with other studies [2,14]. We found that meningiomas were more common in females (F:M ratio 1.83:1) as in other studies [15]. The most common location was the convexity dura as noted by Joseph *et al.* but Wolfsberger *et al.* had almost equal numbers in the convexity and skull base but lower percentage of spinal tumors [2,13]. Proportion of spinal tumors was in concordance with some studies [16,17] but one study from our country showed a low percentage as in study by Wolfsberger [2,14]. The percentages of grade I and II tumors are comparable with those from some other studies [13,14,18]. Wolfsberger *et al.* and Omulecka *et al.* observed a higher percentage of Grade II meningiomas [2,19]. Grade II tumors were more in males which is in accordance with most previously published data but Joseph *et al.* found no significant difference [13, 20, 21].

The commonest subtype was transitional in our study, but results vary across the world.

Immunohistochemistry for PR was positive in 65/68 tumors (95.6%). Some studies including one from another part of India showed a lower percentage of PR positive tumors [15] while a study from Iran revealed similar results as our study [11]. PR positive tumors were more common in females and among grade I tumors as noted in other studies. One factor contributing to this maybe the higher number of grade II tumors in males and a resultant lower average positivity for PR. PR expression according to subtype of meningiomas was not significant as opposed to some studies [15]. Another study from India could not find any statistical significance between PR expression and grade or subtype of meningioma [22]. A high rate of PR positivity irrespective of tumor grade suggests that PR receptor expression maybe used even in the diagnosis of meningioma in difficult cases. A study by Iplikcioglu *et al.* concludes that tumor grade and not the PR status correlates with the biological behaviour of meningiomas [23].

ER positivity was very infrequent and weak as illustrated by other studies [24] and we could not find any correlation between ER positivity and grade of tumor or recurrence. Omelucka *et al.* observed ER positivity in 48% of meningiomas [19]. Average MIB-1 labeling index was lower in our cases as compared to the Iranian group in both grade I & II tumors but the was comparable with the Grade II tumors of Wolfsberger *et al.* and Mukherjee *et al.* [2,16].

Three tumors recurred during our follow up period. All were strongly PR positive. We could not make a meaningful interpretation as regards the correlation between the various clinicopathologic parameters and

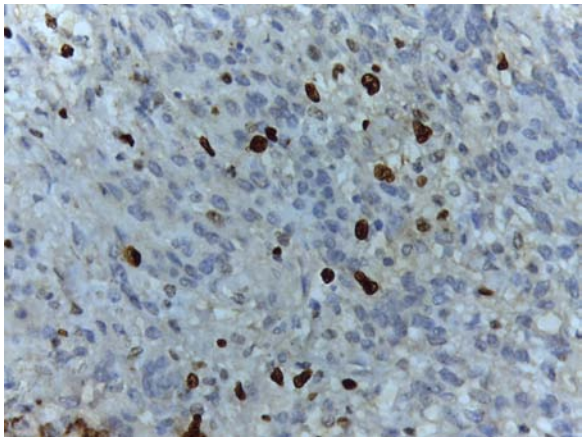

Figure 4: High MIB-1 labeling in an atypical meningioma (MIB-1 X400).

prognosis maybe because of the short follow up period and the low follow up rate.

CONCLUSIONS

Strict follow up of a larger cohort of patients for a longer time period will be required to draw conclusions about prognosis in this population. However, the study clearly shows that the meningiomas occurring in this study population are similar in clinicopathological parameters to those tumors occurring in other parts of the country but different in some aspects like grade with tumors in other parts of the world. Anti-progesterone therapy may be tried as a last option in recurrent and residual tumors in this population because of the high rate of PR positivity.

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