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Histomorphological Study And Grading Of Meningiothelial Neoplasms Using Ki 67 Proliferation Marker, Comparative Study Of Behavioral Outcome In Cranial And Extra Cranial Meningiomas At A Tertiary Care Centre

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Abstract

Background:Meningeal neoplasms are slow growing tumors arising from meningothelial cells of arachnoid matter. It constitutes about 36% of all CNS tumors and are driven by chromosome 22q alterations (e.g. NF2, SMARCB1) and arise in neural crest cell derived meninges. Over 15, WHO morphological variants have been described. Common clinical symptoms include headache, weakness, and visual disturbances. Prognosis of the cases depends a large extent on histological subtypes, Ki 67, extent of surgery,atypical features, chromosomal loss and associated mutations. Somatostatin receptor 2a, epithelial membrane antigen (EMA) and Progesterone receptors are specific marker of meningioma.

Methods:The study comprised of a retrospective analysis of biopsy specimens of meningiomas that was studied over a period of 2 yearsat a tertiary care centre.

Histologial categorization and Ki 67staining were done and studied in correlation with various paramenters of importance like site,recurrence,presenting symptoms and signs, clinical outcome. Conclusion:Meningioma grade I was more prevalent and had a benign biological behavior while grade III was least prevalent in our study and showed recurrence, brain invasion and atypical histological features. Extra cranialbehaved more aggressively and constituted 5 %. Most of recurrent meningiomas were in the atypical meningioma category or WHO grade III category. Few symptoms and signs also varied with particular histological subtypes.

Histological variants and MIB index correlated well in our study.Hot-spot based examination was done and in patients with higher Ki 67, close follow up was done and showed significant

3recurrence (grade III). It is highly recommended that Ki67 need to be assessed in all cases of meningiomas in addition to pattern analysis, to know the biological behavior pattern.

Keywords: Meningioma, Mitosis, Tumor, Grade.

Key message: MIB assessment to know behavioral outcome in plays an important role in patients of low socioeconomic strata, where financial constraint s are seen for cytogenetic studies. Grade III meningioma showed significant recurrence, and extra cranial meningiomas with high MIB had poor outcome and recurrence

Introduction

Meningiomas represent the second most common central nervous system neoplasms in adults and account for 26% of all primary brain tumors (1).They comprise the most common primary intracranial tumors and are usually dura based, often found adjacent to venous sinuses and duralinfoldings. Although most are benign, between 5% and 15% of meningiomas are atypical (grade II) whereas 1–2% are anaplastic meningiomas (grade III). Grade II and III meningiomas show a greater tendency than grade I tumors to recur and metastasize. The current WHO scheme recognizes 15 histologic subtypes of meningiomas. Nine of these are WHO grade I, three are grade II, and three are grade III. In addition to these histologic subtypes, meningiomas can also be graded on the basis of mitotic activity, evidence of brain invasion, growth pattern cellular density, nuclear atypia, and

necrosis. Although histological grade is the most relevant prognostic factor, there are some unusual cases in which establishing a diagnosis of high-grade meningioma following 2020World Health Organization (WHO) histological criteria is extremely difficult (1). Histologic anaplasia and extracranial metastasis are established criteria but the former is difficult to define and the latter represents a clinical finding. Malignant meningiomas, as defined traditionally, are histologically and clinically heterogeneous. Non anaplastic invasive meningiomas of the brain are associated with recurrence and mortality rates similar to those of atypical meningiomas in general (WHO Grade II)(3).Despite a favorable outcome for most patients with WHO Grade I meningiomas, a subset of these patients will have recurrent or progressive disease that advances to a higher grade and requires increasingly aggressive therapy(4). Hot-spot based examination of immunohistochemically stained histological specimens is one of the most important procedures in pathomorphological practice. Thus, a full context-based analysis of histological specimens is also needed in the quantification of immunohistochemically stained specimens. One of the most important reactions is the Ki-67 proliferation marker in meningiomas (6). Loss of the long arm of chromosome 22, which is usually associated with inactivation of the NF2 gene, is the most common genetic abnormality found in meningiomas(5)

Therefore, the aim of the present study is to evaluate the predictive value of Ki-67 (MIB) labeling index,predicting tumor recurrence and overall survival in patients with high-grade meningiomas and to study the clinicopathological correlation in skull based and extra -skull based meningioma

Materials and Methods

The study comprised of a retrospective analysis of biopsy specimens of meningiomas that was studied over a period of 2 years from January 2015 to December 2017in the Department of Pathology of a tertiary health care hospital.A total of 60 patients (with meningiomas of grade I, II, III, atypical meningiomas and anaplastic meningiomas) were evaluated for demographic, clinical, radiological, therapeutic variables and for Ki-67 immunohistochemistry. The criterion for inclusion was the availability of all relevant details. Cases with inadequate history and clinical details, inadequate biopsies and improper fixation were excluded from the study. In accordance with the WHO classification scheme and our own beliefs, meningeal

hemangiopericytomas were also excluded (3). The clinical history & endoscopic findings were retrieved from medical archives. Attempts were made to obtain slides from all known surgeries, including earlier and subsequent resections at the institution. All histologic variants of meningioma listed in the revised WHO 2020 were considered acceptable. The recently described rhabdoid variant was also included. Brain invasion was characterized by an irregular tumor/parenchymal interface without intervening leptomeninges. Histologically borderline samples were accepted if they demonstrated entrapped intertumoral glial fibrillary acidic protein (GFAP)-positive glial processes. Frank anaplasia was defined by either ≥20 mitotic figures in 10 consecutive 0.16 mm2 high power field (HPF) (≥12.5 mf/mm2) or histology resembling carcinoma, sarcoma, or melanoma focally.The cut-off of 20 mitotic figures per 10 HPF represented a natural breakpoint in the distribution of mitotic indices from our prior study and was selected as a representation of excessive tumoral proliferation associated with anaplasia. Cases no longer recognizable as meningioma by routine light microscopy were accepted for study if they demonstrated typical morphology on prior biopsy or showed meningothelial differentiation immunohistochemically or ultra-structurally or by both methods. Brain invasive meningiomas were considered “otherwise atypical” if they were associated with ≥4 mitotic figures per 10 HPF or at least three of the following features: sheeting, macro nucleoli, hypercellularityand small cells. Brain invasive meningiomas without features of anaplasia or atypia were designated “otherwise benign”(3).

Histologic Parameters- 10 morphologic parameters were evaluated namely:cellular pleomorphism, nuclear atypia, macronucleoli, small cell formation, sheeting architecture, necrosis, atypical mitoses, brain invasion, maximal mitotic count per 10 HPF (1 HPF = 0.16 mm2)at hot spots, and maximal cell count across a 1-HPF greatest dimension with hyper cellularity defined as ≥53 nuclei. The first six of these were scored as absent, present, or extensive (i.e., present in ≥50% of sampled tumor). Foci of necrosis were stratified further according to the presence or absence of palisading, whereas atypical mitoses and brain invasion were recorded simply as either absent or present.Histologicsections were reviewed and the histologic subtype, grade, mitosis, presence or absence of necrosis were documented. In cases of neuroinvasive meningiomas, special emphasis on mitotic counts (average of 50 fields), nuclear atypia and presence/absence of necrosis were given and noted. All the tumors were graded according to WHO 2020(1).Immunohistochemistry was performed using Ki-67(MIB) as marker to know the proliferation index. MIB index was tabulated with histologic subtypes. All brain invasive meningiomas, recurrent meningiomas were classified as atypical (Grade II) meningiomas. Meningiomas with 0-4 MIB index were classified as Grade I, 4-20 as Grade II and more than 20 as Grade IIImeningiomas.

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Clinical Parameters

Clinical data was obtained through a combination of chart review, mailed patient questionnaires, and correspondence with clinicians and pathologists. All aspects of the study were approved by Institutionalscientific committee and ethics committee. Parameters recorded included date of birth and death, gender, symptoms, sites of disease, dates of surgery for primary and recurrent tumors, gross total resection (GTR) versus subtotal (STR) resection, dates of radiographic tumor recurrenceand dates of radiation therapy (RT). Extent of resection was based on the neurosurgeon's impression as well as postoperative imaging when available. Data sometimes were incomplete in consultation cases. Survival time was calculated using the first resection date associated with malignancy as the reference point.

MIB-1 Labeling Indices

Immunohistochemical staining for Ki-67 with the monoclonal antibody MIB-1 (Immunotech, Westbrook, ME) was performed in 62 meningiomas (few had come with recurrence which were later counted as a single case, revised actual cases being 60) for which paraffin blocks were available, as described previously.Microwave antigen retrieval and Manual IHC staining were used. Labeling indices from regions of maximal immunoreactivity were quantitated by light microscopy and counting mitosis at areas of high cellularity (hot spots) and were expressed as the percentage.Our previously determined cut-off of 4.0% was used as a measure of high proliferative index. A labeling index ≥20% was defined further as a measure of excessive tumoral proliferation.

Statistical Analysis: Collected data was coded and entered into SPSS version 11.5 and analyzed. Chi Square test was used for the comparison across the groups and $p< 0.05$ was considered as statistically significant.

Results:

The age group of presentation varied from 34 years to 77 years,with average age group being 54 years with slight preponderance in females 26/33 = 0.78 :1. Extra cranial meningiomas constituted only 5%(3/60 cases) while cranial dural constituted 95% (57/60 cases) [Table 1& 2].

Table 1: Details of Extracranial Meningiomas

Serial no	AGE	SEX	CLINICAL DIAGNOSIS	WHO GRADE	MIB%	HISTOLOGICAL TYPE	SITE
1	40	Data Unavailable	C1-C2 Meningioma	I	1	Meningiothelial	C1-C2 Spine
2	65	Female	Meningioma	I	2	Transitional	T10 Spine
3	75	Male	C2-C3 Meningioma	I	2	Meningiothelial	C2-C3 Spine

Table 2: Details of Intracranial/Dural Meningiomas

Variables	*Total(n =57) (%)*	*Grade*			Brain invasion
		I (n = 40)(%)	*II (n = 14)(%)*	*III (n = 3)(%)*	Total (n = 57)(%)
Age in mean (range in yrs)	*56.91 (34-77)*	*54.20 (34-77)*	*55.57(38-73)*	*45 (34-59)*	40
Sex					
Female	32(56.14)	24(75)	7(21.8)	1(3.12)	0(0)
Male	25(43.85)	16(64)	7(28)	2(8)	1(100)
Location					
Convex/cerebral	40(70.1)	26(65)	11(78.57)	3(100)	0(0)
Parasagittal	5(8.7)	5(12.5)	0(0)	0(0)	0(0)
Sphenoid	2(3.5)	2(5)	0(0)	0(0)	0(0)

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Falx/falcine	3(5.2)	2(5)	1(7.1)	0(0)	0(0)
Tentorial	0(0)	0(0)	0(0)	0(0)	0(0)
Miscellaneous	7(12.3)	5(12.5)	2(14.2)	0(0)	0(0)
Subtype					
Meningothelial meningioma (MM)	17(29.82)	14(35)	3(21.4)	0(0)	0(0)
Transitional meningioma (T M)	15(26.31)	15(37.5)	0(0)	0(0)	0(0)
Psammomatousmeningioma(PM)	3(5.2)	3(7.5)	0(0)	0(0)	0(0)
Fibroblastic	1(1.7)	1(2.5)	0(0)	0(0)	0(0)
Angiomatous	4(7.01)	4(10)	0(0)	0(0)	0(0)
Syncytial	1(1.7)	1(2.5)	0(0)	0(0)	0(0)
Choroid	1(1.7)	1(2.5)	0(0)	0(0)	0(0)
Atypical	8(14.02)	0(0)	8(57.14)	0(0)	1(100)
Clear cell meningioma	2(3.4)	1(2.5)	1(7.14)	0(0)	0(0)
Anaplastic Meningioma	4(7.01)	0(0)	2(14.28)	2(66.67)	0(0)
Papillary	1(11.7)	0(0)	0(0)	1(33.33)	0(0)

9 Out of the total of 60 cases, 40 were graded as grade I meningioma, 14 as grade II and 3 as grade 3 meningiomas based on Ki-67 labelling index(LI).Grade I comprised of Ki-67 labelling index of 0-4%, grade II comprised of 4-20 % and grade III comprised of >20 % [Table 3].

Table 3: Grades of Meningioma based on Ki-67 labelling index.

Parameters	Ki-67 Labelling index	Grade I	Grade II	Grade III
1	**0-4 %**	**31**	**8**	**1**
2	**4-8 %**	**6**	**2**	**1**
3	**8-12%**	**2**	**2**	**0**
4	**12-16 %**	**1**	**1**	**0**
5	**16-20 %**	**0**	**0**	**1**
6	**>20 %**	**0**	**1**	**0**
	TOTAL	**40**	**14**	**3**

The different histologic subtypes of meningiomas were also studied with respect to the most common presenting symptoms(Table 4,Table 5 & Table 6).

Table 4:Correlation of Histologic Subtypes of meningiomas(Grade 1) with the presenting symptoms

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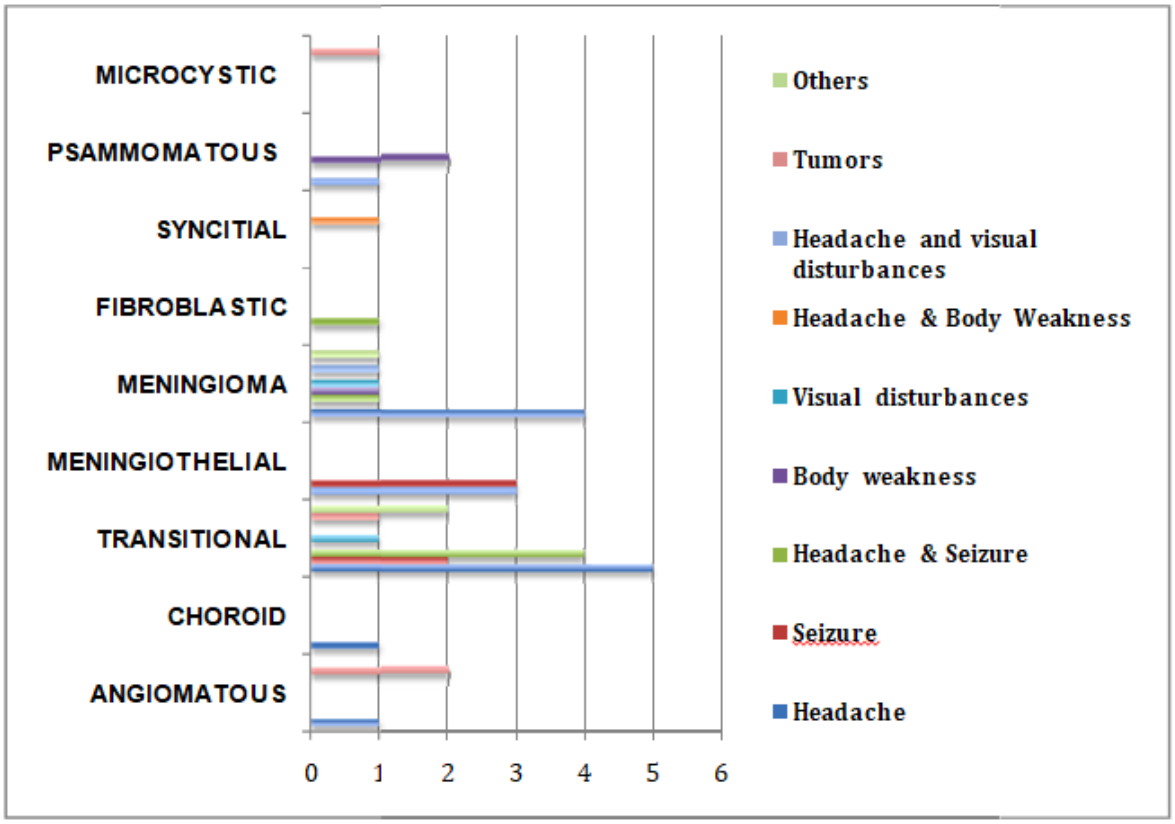

Table 5: Correlation of Histologic Subtypes of meningiomas (Grade II) with the presenting symptoms

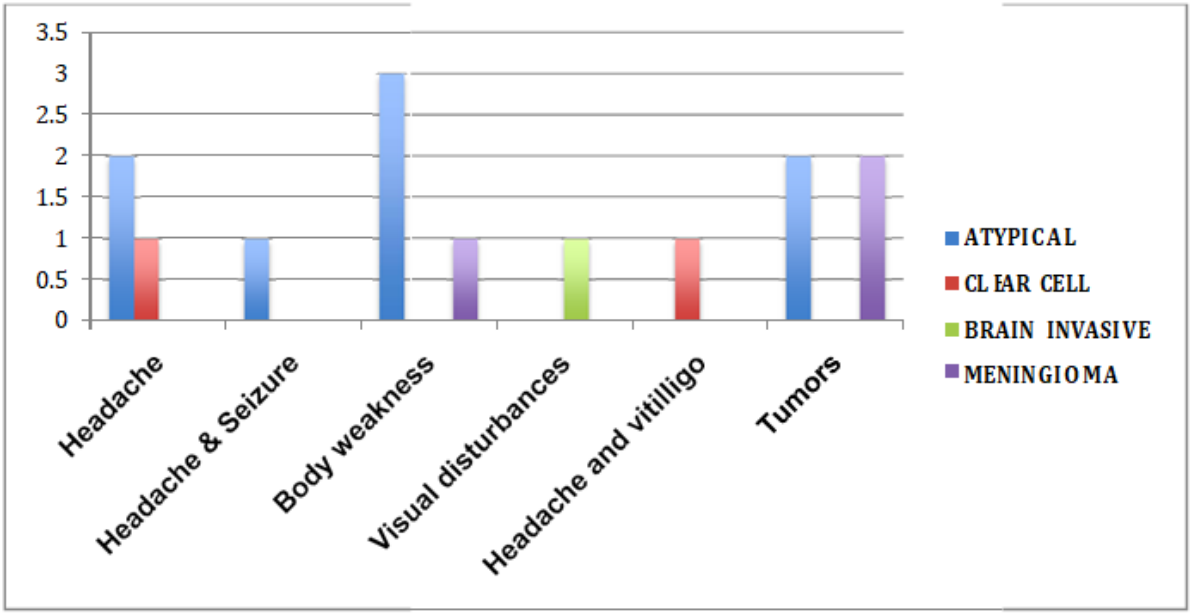

Table 6: Correlation of Histologic Subtypes of meningiomas (Grade III) with the presenting symptoms

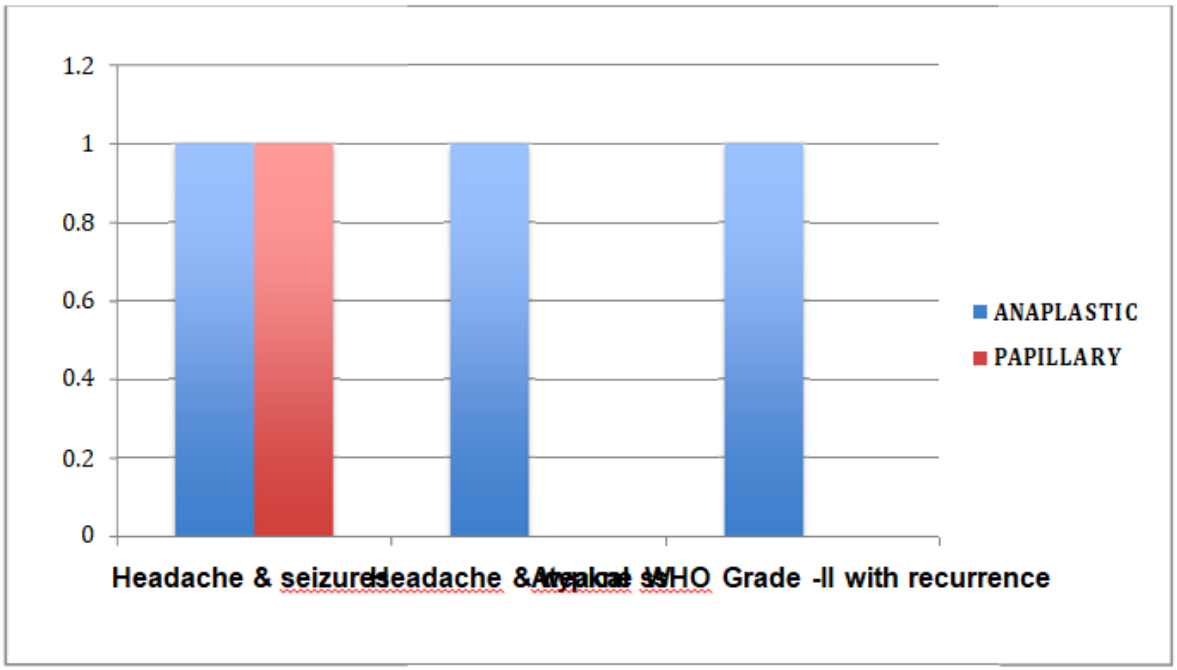

Table 6: Histological subtypes of Meningioma with symptoms

CLINICAL REPORT	HISTOPATHOLOGICAL REPORT	GRADE	MIB%	DURAL/EXTRA DURAL
Meningioma	Brain invasive	II	2.5	Dural
Recurrent meningioma	Recurrent transitional	I	2	Dural
Recurrent meningioma	Atypical	II	3	Dural
Recurrent atypical	Transitional	I	2	Dural
Suspected metastasis	Atypical	II	14	Dural
Suspected metastasis	Transitional	I	2	Dural
Meningioma with scalp liopma	Atypical	II	11	Dural
Meningioma with other malignancy	Meningothelial (“resected margin touch the tumor;”)	II	1.5	Dural
With secondaries	Meningothelial	II	1.5	Dural
Atypical	Anaplastic	III	4	Dural
Cystic	Angiomatous	I	2.5	Dural

Discussion

Meningiomas are benign indolent neoplasms, with a subset of them being aggressive with a higher tendency to recur despite radical surgery. Certain histological characteristics have stronger associations with a decreased recurrence-free survival (5)In the present studymost cases were seen in the 4th and 7th decade. A majority of 53.3% cases were seen in the range of 4th to 6th decades and between 5th and 6th decade, 28.3% cases were seen which was the maximum for a single range.These statistics are similar to a study done by Solanke et.al(8).Female predominance was seen to be 55% and this was similar to the results obtained in a study conducted by Telugu RB etal(9).

Extra Dural Meningiomas

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Extra duralmeningiomas are a rarer type compared to dural meningiomas. Pure spinal meningiomas are very rare. Of the observed 3 cases of Extradural meningiomas, all were of WHO Grade 1, had MIB% values less than 4%, with C2 spinal involvement was seen in 2 cases.Clinically they were diagnosed as meningiomas with histological types of transitional meningioma and meningothelial meningiomas with the latter being more in number. In a previousstudy, similar to the present study most of the extradural meningiomas were of WHO Grade 1 and of meningothelial type(10).The common complaints experienced included pain in the neck, generalized weakness and progressive paraparesis. Compared to the study done by Solanke et al where most of the extracranial lesions were in thoracic spine, we encountered involvement of cervical spine involvement more frequently (8). However this study was limited due to the less number of cases of extradural meningioma.

Dural Meningiomas

In duralmeningiomas, the most common site(cerebral convexity) of meningioma were statistically significant similar to the observations by Babu et al (11). In our study the most common morphological type overall was meningothelial type (29%) followed by transitional (26%).The recently described rhabdoid variant (papillary meningioma with focal rhabdoid) fell into transitional type as a grade III meningioma, it however had MIB% of 1-1.5%.In the present study, 77.5% (31 of 40 Grade I cases) fell into the range of 0 to 4% of Ki-67, 42.8% of grade II cases had Ki-67 scores between 4 to 20; and grade III meningiomashad a varied distribution and 3 cases fell into 3 different Ki-67.Mean Ki-67 in brain invasive meningiomas was 9.56 %(only 1 case was observed) and in non-brain invasive meningiomas was 8.08 %.Some authors have found a higher mean MIB-1 LI in meningioma that ultimately recurred, while others have 13obtained different result. In this study, Ki-67 LI contrasted with grade of meningioma from grade I to III displaying their aggressive nature, to the observations by Devaprasath A et al. and by Amatya et al(12,13).

Clinical Features:

GRADE I

The most common complaints were headache, seizures and body weakness. Headache and seizures solitarily or combined were the chief complaints in Transitional meningiomas. Seizures alone were more common in Meningothelial meningioma. Tumors presentation as mass was the sole feature in microcystic type and common in angiomatous meningioma.

Transitional meningioma was observed to have a wide spectrum of clinical features including headache, seizures(GTCS type), body weakness, visual disturbances, tumors per se, lower limb weakness and pain.

GRADE II

Atypical meningiomaswere more common here with most of them manifesting with chronic generalized body weakness. Certain atypical meningiomas manifested as tumor per se, causing headache and seizures.Clear cell meningiomas were observed to produce vitiligo along with headache. One case of brain invasive meningioma with optic nerve atrophy was seen.

GRADE III:

Amongst Grade III meningiomas, the most common type was anaplastic meningioma which manifested as headache with seizure or generalized weakness. Recurrence of Grade II Atypical meningiomas was also seen in

Grade III Anaplastic dural meningiomas.Papillary meingioma with focal rhabdoid features, manifested as headache with seizures.

Grade I tumourwere treated with surgery alone, whereas Grade II and III were treated with surgery, radiotherapy and chemotherapy.

Comparing Recurrent/Brain Invasive Meningiomas with MIB%

Out of 11 cases, most of the recurrent meningiomas were of grade II (6 cases; 54%) and the mean MIB% of these grade II meningiomas was 5.33%. This co-related with the range of 4-20% used to include grade II meningiomas. All of them were dural type.

Currently in atypical meningioma with brain invasion, mitosis and MIB is of limited use and morphology with brain invasion is considered as per WHO guidelines, 2020

Our initial implications were to expect a strong correlation between MIB% and the grading of meningioma with higher the grade and greater the severity; and that extradural meningiomas being more severe than dural. Most of the low-grade meningioma (Grade I) had a consistently low Ki-67 score.Recurrence was correlating with

higher MIB.However,wehave not emphasized on the time interval of recurrence in relation to KI67%. Ki-67 PI was a marker for time to recurrence rather than a predictor of recurrence in few studies. (5)

Literature search showed cases of combination of histological variants as reported by Habib and kaani. Mixed Rhabdoid and papillary architecture was seen in one case with diffuse infiltration of leptomeninges and spinal cord metastasis. However we did not encounter cases with mixed histological features.

CNS WHO grade III can be applied to all meningiomas with either TERT promoter mutation or CDKN2A/B homozygous deletion.(13) Pathologic classification alone with Ki- 67 as in our study has limitations and all meningiomas require triple tests-histomorphological, immunophenotypic and cytogenetic analysis to assess the biological behavior of the tumor. Gain of genetic material on chromosome 1q,9q,12q,15q,17q,20q and loss in short arm of chromosome 1p,4p,6p,9p 10,14q,18q and 22q have been documented. About 80% of meningiomas show loss of chromososme 22q where NF2 gene is located and is the most common chromosomal abnormality. (14,15)15

Conclusions:

We attempted to study Ki- 67 expression in skull based and extra skull based meningiomas and to have correlation with Ki-67 labelling index and grades as well as incidence of recurrence and survival based on the index. Cranial meningiomas that occur outside of the skull base are more likely to have a higher MIB-1 labeling index and recur with a higher grade than those within the skull-based lesions, suggesting that non–skull based cranial tumors may have a more aggressive biology than skull-based tumors. Although brain invasive meningiomas were categorizedas grade III, aggressive as per WHO 2016,lesser mitotic rates were found (2.6% in our case) and without recurrence or revisits by patient, variations aptly discussed in WHO 2020. Mutational analysisof telomerase reverse transcriptase (TERT) or chromosomal studies was not done in our studies due to the financial constraints.

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