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An Analytical Study on the Various Histopathological Features of 250 Cases of Meningiomas and its Relation to the Behaviour of the Tumour

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Abstract

Context: Meningiomas are one of the most common primary central nervous system neoplasms. They occur most commonly in female patients being most common in the fourth and fifth decades of age. They may be of intraspinal or intracranial and extra-axial location. *Aims*: The aim of this study is to highlight the importance of histopathological features in analyzing the behaviour of meningiomas. *Settings and Design*: This is an analytical study undertaken at the department of pathology in a tertiary care hospital for a period of three years from may 2013 to june 2016. *Materials and Methods*: All the clinical data of the meningioma cases were obtained from the patient files in the pathology registers. The hematoxylin and eosin stained and mounted slides were retrieved and reviewed from the archives of pathology laboratory. *Statistical Analysis*: Statistical analysis was carried out using SPSS software version 17. Various tests used in the study were the chi square test and the T test. *Results*: Out of the 250 cases of meningiomas analysed in this study, 92% of the cases belonged to grade I. Features such as small cell change, hypercellularity, sheet like pattern, nuclear pleomorphism, macronucleoli, vesiculous nuclei, necrosis, hypervascularity and brain invasion were seen predominantly in higher grades (GRADE II and III) of Meningiomas thereby proving their association with aggressive behaviour of tumour and their association was statistically significant with a P value of <0.0000001. *Conclusion*: Proper histopatholgical analysis is very important for the diagnosing, grading and prognostication of meningiomas.

Keywords: Meningioma; Atypical Meningioma; Anaplastic Meningioma; Meningioma Histopatholgy.

Introduction

Meningiomas are primary central nervous system neoplasm with an intraspinal or intracranial and extra-axial location [1]. It originates from the arachnoidal (meningothelial) cells and are characterized by attachment to the inner surface of dura mater. Meningiomas comprises of about for 24–30% of all primary intracranial neoplasms and is the second most commonly reported CNS tumor [2]. According to CBTRUS (Central Brain Tumor Registry of the United States),the prevalence of histopathologically confirmed Meningiomas were approximately found to be 97.5/100,000 [3]. Though majority of Meningiomas are benign, they lead to significant morbidity and mortality. Based on the histomorphology of the tumour Meningiomas are classified according to WHO as grade I, II, & III. Though majority of Meningiomas are morphologically classified as benign it was very difficult to predict their behavior as even benign or low grade Meningiomas tend to recur. The aim of this study is -

1. To histopathologically analyse a large number of cases of Meningiomas consecutively operated during a period of three years.
2. To analyse the various histopathological features that can be seen in cases of Meningiomas and their association with the grading of Meningiomas.

Materials and Methods

This is a Retrospective & Prospective study done at a tertiary care hospital for a period of 3 years from June 2013 – May 2016. This study included all the

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intracranial and intraspinal Meningiomas of the three WHO grades. All other tumours of meningeal origin such as hemangiopericytoma, hemangioblastoma and solitary fibrous tumours were not included in the study.

All the clinical data and radiological findings of the meningioma cases were obtained from the patient files in the pathology registers. The hematoxylin and eosin stained and mounted slides were retrieved from the archives of pathology laboratory. All the slides were reviewed and graded according to the histopathological WHO classification of Meningiomas (2007) guidelines without the knowledge of previous grading or patient outcome [4].

The tumour subtyping was done according to the dominant histological pattern (>50%) seen in the microscopic sections of the tumour [5]. The following histopathological parameters such as hypervascularity, hypercellularity, sheet like pattern , mitotic counts, small cell change, macronucleoli, brain infiltration, necrosis, vesiculous nucleoli, nuclear pleomorphism, psamomma bodies, fibrosis, inflammatory cell infiltration, xanthomatous change and bone infiltration were analyzed in this study.

The criteria used for analyzing most of the factors were based on a study done by Thomas Backer-Grondahl et al [6].

Hypervascularity was defined by presence of prominent blood vessels at 10X magnification in 2 or more low power fields [6].

Hypercellularity was analyzed in a semiquantitative manner as present or absent . All the non tumour cell areas such as those with vascular components, lymphocytes, xanthomatous cells, microcystic areas were not included in the analysis of hypercellularity. Sheet like pattern was identified by lack of characteristic growth pattern of Meningiomas seen in more than half of the field area at 10X magnification [6].

Mitotic counts were counted in microscopic fields of tumour with high mitotic activity. Average number of mitotic figures in ten non overlapping consecutive high power fields (40X) were obtained [6].

Small cell change was identified by presence of increased nuclear cytoplasmic ratio. Nucleoli seen prominently at 10X magnification was considered as macronucleoli [6].

Brain infiltration is identified by presence of tongue like irregular protrusions of tumour cells in to the brain parenchyma without any intervening leptomeninges between the brain parenchyma and the tumour cells infiltrating them [6].

Following treatment of Meningiomas, the appearance of a new radiologically identifiable tumour lesion at the previous site of the tumour is set as a criteria for recurrence [1].

Statistical analysis was carried out using SPSS software version 17. Various tests used in the study were the chi square test for discrete variables .and the T test for continuous variables. A significant association between various factors analyzed in the study was found with a level of significance 95% confidence interval and a P cut off value of less than 0.05.

Results and Observations

In this study about Meningiomas, 250 cases operated during a period of three years were included among which 229 (91.6%) and 21(8.4%) cases were intracranial and intraspinal Meningiomas respectively. The total number of male and female cases in the study were 93 (37.2%) and 157(62.8%) cases respectively. Among intracranial Meningiomas, male patients accounted for 91 cases and female patients accounted for about 138 cases with a male: female ratio of about 1: 1.5 . Among intraspinal Meningiomas, only two cases belonged to male and female patients accounted for about 19 cases with a male: female ratio of about 1:10. The mean age of occurrence of Meningiomas were found to be 48.5 and it did not vary significantly among male and female patients. Maximum number cases were seen in fifth and sixth decade of life. Meningiomas were least prevalent in less than 30 years of age. The convexity Meningiomas (57.4%) that includes those on the convexity, falx and parasagittal regions together constitutes the most common site of occurrence of Meningiomas in this study. The gross appearance of various types of meningiomas are described in figure 1. The various histopathological types of Meningiomas are given below in Table 1. The most common types encountered in this study were meningothelial (40.4%) and transitional Meningiomas (27.2%).

The number of cases in grade I, II & III were 230(92%), 17(6.8%) & 3(1.2%) respectively. Grade 1 or benign Meningiomas were found to be in higher numbers compared to grade II or III Meningiomas. The various histopathological features analyzed among all the three grades of Meningiomas in the study were detailed in Table 2 and Fig. 2.

Features such as small cell change, hypercellularity, sheet like pattern, nuclear pleomorphism, macronucleoli, vesiculous nuclei, necrosis and brain

Table 1: Frequency of occurrence of different histopathological types of meningiomas

Grade	Hpe Types	Frequency	Percentage
Grade I	Meningothelial Meningioma	101	40.4
	Transitional Meningioma	68	27.2
	Fibrous Meningioma	20	8
	Microcystic Meningioma	7	2.8
	Angiomatous Meningioma	16	6.4
	Psammomatous Meningioma	17	6.8
	Lympho plasmacytic Meningioma	1	0.4
Grade II	Atypical Meningioma	14	5.6
	clear cell Meningioma	2	0.8
	Chordoid Meningioma	1	0.4
Grade III	Papillary Meningioma	2	0.8
	Anaplastic Meningioma	1	0.4
Total		250	100

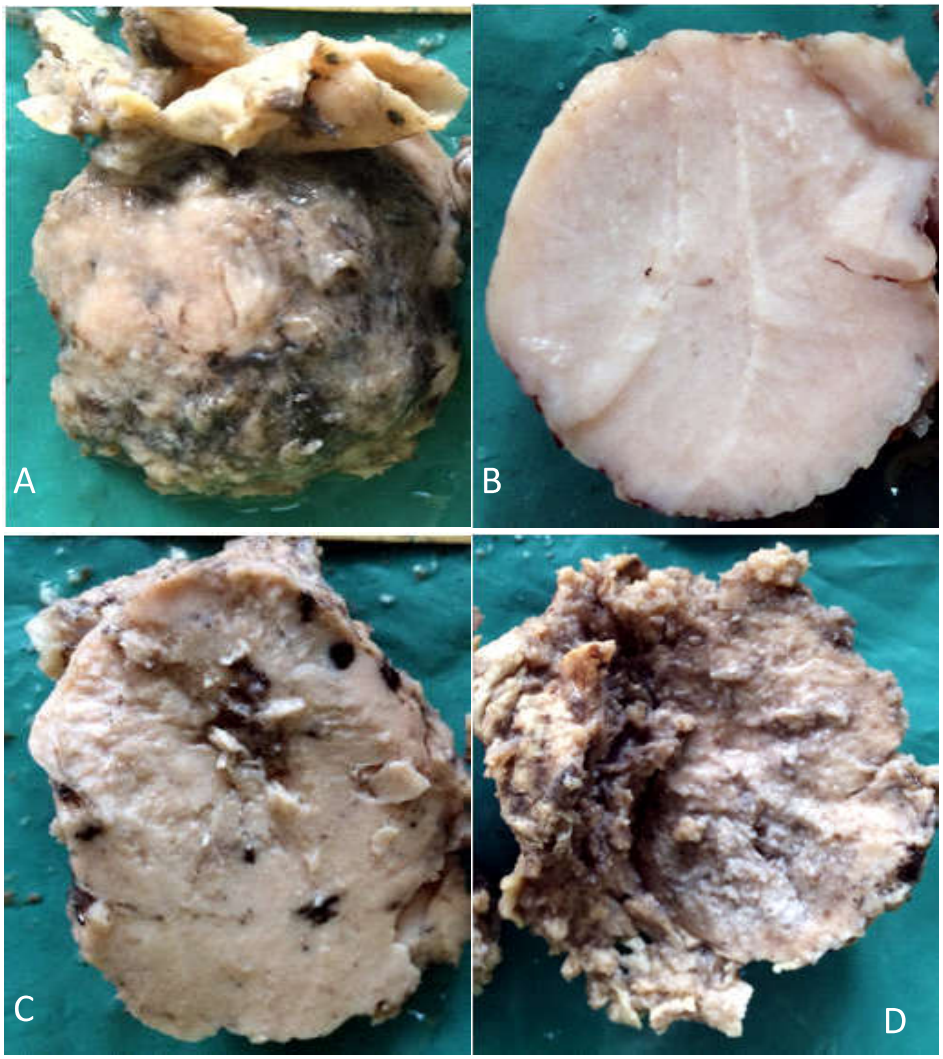

Fig. 1A.: External surface of meningioma showing dural attachment. **B.** Cut surface of grade I Meningioma showing homogenous solid and whorled appearance. **C.** Cut surface of Atypical (grade II) Meningioma showing solid grey white mass with focal necrotic foci. **D.** Cut surface of Papillary (grade III) Meningioma showing large solid, friable mass with papillary projections with necrotic and hemorrhagic areas

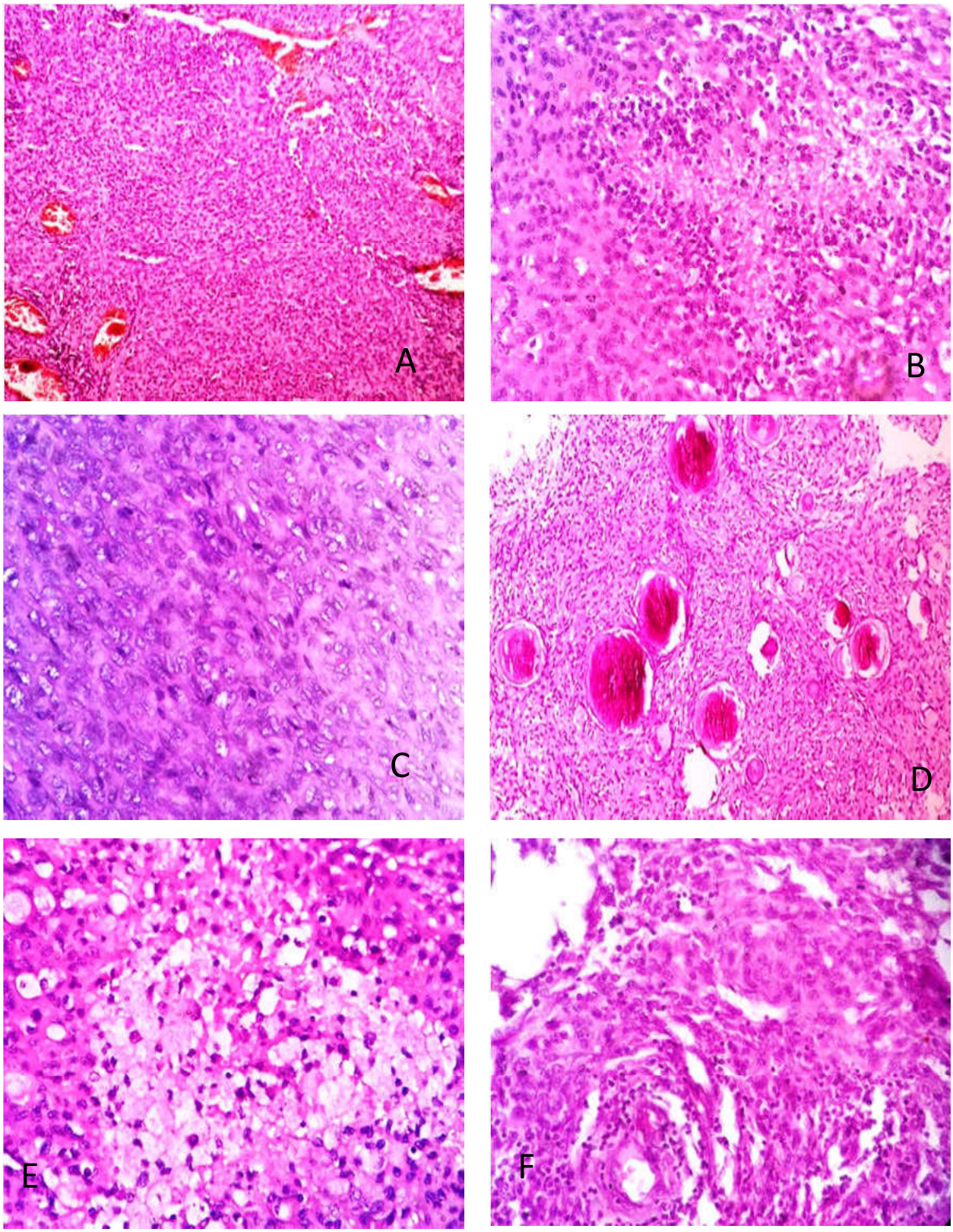

Fig. 2: Shows the various histopathological features analysed in this study **A.** Shows hypercellularity,sheet like pattern and hypervascularity in an atypical meningioma (H&E,100X), **B.** Shows areas of necrosis (H&E,400X), **C.** Shows increased mitotic figures in anaplastic meningioma(H&E,400X), **D.** Shows the presence of psamomma bodies(H&E,100X), **E.** Shows foamy cell change in meningothelial meningioma(H&E,400X), and **F.** shows lymphocytic infiltration in transitional meningioma(H&E,400X).

Table 2: Comparison of various histopathological features in different grades of meningiomas and the statistical association of these features with benign grade i meningiomas and high grade (grade ii and iii) meningiomas

Histopathological Feature	Grade I Number of cases(% to total grade I cases(191))	Grade II Number of cases(% to total grade II cases(16))	Grade III Number of cases(% to total grade III cases (2))	P Value
Sheet like pattern	40 (20.8)	15 (93.8)	2 (100)	<0.0000001
Hypercellularity	23 (12)	16 (100)	2 (100)	<0.0000001
Small cell change	5 (2.6)	7 (43.8)	2 (100)	<0.0000001
Macronucleoli	0 (0)	3 (18.8)	1 (50)	<0.0000001
Necrosis	0 (0)	9 (56.3)	2 (100)	<0.0000001
Brain infiltration	0 (0)	10 (62.5)	2 (100)	<0.0000001
Nuclear pleomorphism	0 (0)	6 (37.5)	2 (100)	<0.0000001
Vesiculous nuclei	0 (0)	1 (0.5)	2(100)	<0.0000001
Hypervascularity	49 (25.7)	15 (93.8)	2 (100)	<0.0000001
Lymphocytic infiltration	10 (5.2)	2 (12.5)	0 (0)	0.4539
Foamy cell change	12 (6.3)	2 (12.5)	0 (0)	0.5853
Psamomma bodies	144 (75)	1 (0.5)	0 (0)	0.000001
Fibrosis	148 (77.1)	2(12.5)	0 (0)	0.000001

Table 3: Frequency of occurrence of different histopathological types of meningiomas between the present study and a study by ramesh babu telungu et al

Various types of meningiomas	Present study (%)	Ramesh babu telungu et al [67] (%)
Meningothelial	40.4	23.6
Transitional	27.2	17.85
Fibrous	8	12.5
Microcystic	2.8	2.67
Angiomatous	6.4	4.91
Psammomatous	6.8	14.28
Secretory	-	0.44
Lympho plasmacyte- rich	0.4	-
Atypical	5.6	1.33
Chordoid	0.4	-
Clear cell	0.8	1.33
Papillary	0.8	2.23
Anaplastic	0.4	0.52

invasion were seen predominantly in higher grades (GRADE II and III) of Meningiomas thereby proving their association with aggressive behaviour of tumour and their association was statistically significant with a P value of <0.0000001. Though hypervascularity was seen in some of grade I Meningiomas, their association with high grades of Meningiomas were statistically significant with a P value of <0.0000001.

The mean mitotic figures per 10 high power field were 0.9, 6, 22 in Meningiomas of grade I , II and III respectively. There by showing increased mitotic rates is associated with higher grades of the tumour.

Xanthomatous /foamy cell change of the tumour cells was seen in Meningiomas irrespective of their grade. Most of these cases were found to have hypervascularity with the foamy cells arranged around the blood vessels. Their presence did not affect the grades of tumours and their association was not statistically significant with a P value of 0.5853.

Lymphocytic infiltration in tumour was seen in Meningiomas irrespective of their grades. Hence their association was statistically insignificant with a P value of 0.4539 and were in no way found to play a role in the tumour severity.

Psamomma bodies were seen more commonly with grade I tumours and their presence was associated with increased fibrosis among the tumor cells. Most of the Meningiomas of intraspinal location were found to have increased number of psamomma bodies. Psamomma bodies and fibrosis were more commonly found in grade I rather than grade II and III tumours and was found to be statistically significant with a P value of 0.000001.

Hence the various histopatholgical features of meningiomas and their association with the grading and behaviour of the tumour have been studied.

Discussion

Meningiomas are one of the most common primary central nervous system neoplasms. They occur most commonly in middle-aged and elderly patients. There is a higher incidence of these tumours among female patients with a female:male ratio of 3.5:1 [7]. Female predominance is even more prominent in cases of Spinal Meningiomas. Atypical and malignant Meningiomas shows a slight higher male predominance [8].

Meningiomas are slow growing tumours that may be asymptomatic being diagnosed incidentally or during autopsy [9]. They produce focal neurological deficit's such as Seizures, hearing loss, visual changes, paresis, and headache with obstructive hydrocephalus due to compression of adjacent structures.

Among the various risk factors that have been enumerated for the development of meningiomas, the most notable ones are exposure to ionizing radiation and hormonal influence. Exposure to ionizing radiation is the primary and the important risk factor associated with the development of Meningiomas. The risk of development of Meningiomas increases by 6 to 10 folds upon radiation exposure [10]. Meningiomas shows various clinical and epidemiological features that suggests the role of female sex hormones in their development. For example, females show an increased incidence of Meningiomas and it occurs rarely before puberty or after menopause, corresponding to the reproductive years with time of maximal hormonal activity . There is a regression or decrease in size of these tumours on cessation of hormonal replacement therapy [8].

The most common mutation associated with Meningiomas are inactivation and deletion of NF2 on chromosome 22.The other genomic alterations that are recurrently seen in Meningiomas includes loss of chromosomes such as 1p, 9p, 6q, 10q, 14q, and 18q [11,12]. Several familial cancer predisposition syndromes that includes NF1, VHL, PTCH, PTEN, and CDKN2A genes are associated with the occurrence of Meningiomas [13]. But the role of these genetic abnormalities in the development of Meningiomas are still not unknown.

More than 80% of Meningiomas are supratentorial in location. The most common sites are falx cerebri, parasagittal, over cerebral convexities, sphenoid ridge, olfactory groove, para and suprasellar region, tentorium cerebelli, foramen magnum, spinal canal and cerebellopontine angle [14]. Less common sites includes those arising from the choroid plexus and CNS parenchyma itself [15]. Spinal Meningiomas most commonly occurs in the thoracic region. Malignant Meningiomas most often metastasizes to liver, bone, lung and pleura [4].

One of the important radiological characteristics of Meningiomas are presence of dural tail surrounding the perimeter of dura around the mass. According to study done by New et al in 1982, imaging features such as central areas of tumour necrosis,peritumoral odema, bony destruction, indistinct brain and tumour interface (interdigitation of tumour with brain) and mushrooming(prominent tumour or pannus, extending away from the globoid tumour mass with extensive perifocal oedema) have been described to be associated with aggressive nature of tumour pointing to their malignant behaviour [16].

According to WHO, Meningiomas are classified as benign (grade I), atypical (grade II) and anaplastic (grade III). The 2000 revision of 1993 WHO classification of Meningiomas made the definitions for grade II and grade III Meningiomas more objective and reproducible [8]. This resulted in a great shift in the number of cases diagnosed as grade II Meningiomas from 5 to 7% by 1993 classification to 20 to 38% by 2000 classification [17] .

The previous WHO classification (2000) of Meningiomas were little changed and recently updated in 2007. The major difference that was made was brain infiltration is considered now as a criteria for classifying a tumour as grade II or III. Those tumours that otherwise possessed benign morphology but had brain infiltration would now be graded as grade II [4].

Majority of Meningiomas fall under grade I accounting for about 80 to 90%. The diagnostic criteria for grade I meningiomas includes presence of mitotic figures about <4/10 high power field (hpf) [4]. The most common types among these are meningothelial, transitional and fibrous Meningiomas. They exhibit a relatively low rates of recurrence (7 to 20%) and are less aggressive in behaviour . On the other hand, site of the tumour has a major impact on the prognosis of Meningiomas. For example:- convexity Meningiomas are completely curable by surgical resection where as those situated at skull base such as petroclival area have a slow but invasive and destructive growth causing erosion of bony structures. These tumours may remain histologically benign for long time or transform to higher grades over years [4]. Though these tumours have benign cytological features they have tendency to invade brain, dura and it's sinuses, skull, and rarely orbit, skin and soft tissues [13] .

The incidence of grade II and grade III meningiomas

includes 4.7% to 7.2% and 1.0% to 2.8% respectively [17]. Grade II meningiomas have mitoses about 4 - 19/10 hpf or the presence of 3 or more of the following five features: 1. increased cellularity 2. uninterrupted pattern less or sheet-like growth 3. small cells with a high nuclear/cytoplasmic ratio 4. prominent nucleoli 5. foci of 'spontaneous' or 'geographic' necrosis. Grade III meningiomas exhibits loss of differentiated features resulting in carcinoma, melanoma or sarcoma like appearances or the presence of ≥ 20 mitoses per10 hpf [4].

Most of the Meningiomas are well-demarcated, firm and rubbery, sometimes presents as lobulated and rounded masses with broad based dural attachment [4]. Some Meningiomas have a gritty appearance, indicating the presence of psammoma bodies. Bone formation is very rare. Atypical and anaplastic Meningiomas are larger than their benign counterparts and may have necrotic changes [4]. Histomorphology of Meningiomas are so diverse that it required a revision in the WHO 2000 to WHO 2007 classification [6]. This study is undertaken not only to analyse the histopathological spectrum of Meningiomas and their grading but also to know about the association of different histopathological features with the behaviour of the tumours.

According to Nasrin shayanfar et al and Thomas Backer-Grondahl et al [6,18] the first 3 most common types of, Meningiomas were meningothelial, transitional and fibrous types and this correlates well with this study also. The distribution of various types of Meningiomas in this study parallels the finding in other studies also such as done by Thomas backer at al, Willis J et al and Uzum N et al [17,19]. Comparison of the frequency of occurrence of the different histopathological types of Meningiomas among various studies as given below in table 3. The minor differences in the proportion of cases in each type of Meningiomas between the current study and study done by ramesh babu telungu et al [20] may be due to subjective error in the grading of the tumour.

The grade I or benign Meningiomas were most frequently encountered in all the studies. Except for a slight degree of variation in the proportion of cases among various grades, this study goes well with most other studies done by Thomas backer- grondahl et al, Arlete hilbig et al, Nasrin shayanfar et al, Norden et al and Ramesh babu telungu et al with regard to the three grades of Meningiomas [6,18,20,21,22].

As assessed in this study, the mutual correlation between high grade Meningiomas and the histological features such as small cell change, sheet like pattern, high mitotic counts, necrosis, prominent nucleoli and hypercellularity has also been positively correlated by Thomas backer et al [6] in 2012 in their study on histopathological spectrum of meningiomas. These five histopathological features that were used assess the aggressive behaviour of Meningiomas are together called as "soft criteria" [6]. Presence of these features along with increased mitotic activity in the tumour cells points to aggressive nature of the tumour and they should be labelled as high grade Meningiomas. Presence of atleast one of the above features in an otherwise benign Meningiomas should prompt the labelling of these tumours as "benign meningioma with atypical features" [6] and the other associated features for a high grade tumour must also be carefully searched for. The various confounding factors faced during analysis of these soft criteria deserves a special mention. The small cell change was difficult to access in certain foci of tumour that had inflammatory cell infiltrate, apoptotic changes and in those cells found in close proximity to necrosis. The normal syncytial pattern of growth of Meningiomas, hypervascularity and inflammatory infiltrates in some Meningiomas simulated a sheet like architecture or hypercellularity of the tumour.

Regarding necrosis in Meningiomas, they can either be small or large. Most of the large areas of necrosis arising out of radiation therapy or preoperative embolisation were not included in the study. Only those spontaneously occurring micronecrosis arising out of tumour undernourishment or tumor cell hypoxia were accounted.

As said by perry et al, those nucleoli visible at 10x magnification shall be called as macronucleoli was so useful in assessing this feature in the tumours included in this study [23]. Nuclear pleomorphism in tumour cells was seen not as a sign of anaplasia but as a simple degenerative phenomenon [23] by some investigators. But the findings in this particular study correlated the association between nuclear pleomorphism and increased grades of tumour.

In a study by Thomas Backer-Grondahl et al [6], presence of vesiculous tumour nuclei was positively correlated with grade II meningioma. This study also finds a similar association between vesiculous nuclei and higher grades of Meningiomas.

In this present study hypervascularity was seen more commonly with atypical and anaplastic variants of Meningiomas but they were also demonstrated in good number of cases of grade I Meningiomas such as angiomatous, microcystic and a few cases of meningothelial Meningiomas. Though hypervas cularity was thought to indicate aggressive behaviour of tumour as said in some studies [6], their association

with some benign Meningiomas prevents from considering it as a full-fledged criteria for aggressive behaviour of the tumour.

Mitotic counts are one of the most important criterion to assess the grading pattern in Meningiomas. There are various techniques of assessing the mitotic counts and the most common and simplest method being evaluation for mitotic figures in a normal hematoxylin and eosin stained sections. But this method produces inconsistent results due to interobserver variability and mistaking of pyknotic cells for mitotic figures.

Therefore to ward over this problem, some of the methods that produces more consistent results have been brought in to play such as immunohistochemical staining for Ki67 (MIB-1 labelling) and PHH 3 (phospohistone H3) [24]. This study also finds that increasing grades of Meningiomas had increased mitotic activity in their tumour cells.

The presence of psamomma bodies indicates an increased occurrence of fibrosis in the tumour. The increased fibrosis and collagen deposition seen in Meningiomas have been linked to the production of certain growth factors such as VEGF and EGF by the meningothelial cells [25].

These findings are seen in all Meningiomas irrespective of whether they are benign or high grade meninigiomas as said in few studies [65].

But in this current study of interest both the psamomma bodies and fibrosis with collagen deposition were predominantly seen among benign Meningiomas and their effect on prognosis of the tumour is unknown.

Foamy cell change and inflammatory cell infiltration was seen in almost all grades of Meningiomas in this study and hence had no diagnostic or prognostic significance.

Conclusion

Though majority of meningiomas were thought to be benign, it is very difficult to predict their behaviour. They have increased risk of recurrence especially when found at critical locations in the brain and following incomplete surgical removal. Long standing grade I meningiomas can get transformed to high grade meningiomas.

Grade II and III meningiomas are quite aggressive with increased rates of recurrence following surgical removal. Hence, careful assessment of the histopathological features for better categorization and grading of tumours forms a very important role in the diagnosis and management of meningiomas.

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