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Original Research Paper

Pathology

PROGNOSTIC VALUE OF MIB-1 (KI-67) AND BCL-2 EXPRESSION AS ADJUNCTS FOR GRADING AND PREDICTING AGGRESSIVE BEHAVIOUR IN MENINGIOMAS

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ABSTRACT

Background: Meningiomas are the most common primary intracranial tumours, ranging from benign (WHO Grade I) to atypical (Grade II) and malignant (Grade III) variants. Accurate grading is vital, as a subset exhibits aggressive behaviour and increased recurrence. Immunohistochemical markers MIB-1 (Ki-67, a proliferation index) and BCL-2 (an anti-apoptotic protein) are valuable for distinguishing aggressive tumours. This study correlates histopathological features of intracranial meningiomas with MIB-1 and BCL-2 expression. **Aim:** To evaluate meningioma histopathology, assess MIB-1 and BCL-2 expression, and determine their association with tumour grade, prognosis and recurrence. **Materials and Methods:** This cross-sectional study included 50 histologically confirmed meningioma samples graded by WHO criteria. Immunohistochemistry (IHC) for MIB-1 and BCL-2 was performed. The MIB-1 labelling index was calculated as the percentage of positively stained nuclei, and BCL-2 was assessed based on intensity and proportion of positive cells. Findings were correlated with tumour grade, with $p < 0.05$ considered significant. **Results:** The majority of the 50 cases were 30–59 years (78%) with female predominance (M:F = 1:1.94). Most cases were intracranial (94%), with 82% being WHO Grade I, 4% Grade II, and 6% Grade III. Meningothelial subtype was the most frequent (54%). BCL-2 Expression: BCL-2 positivity was seen in 15 cases (30%). A highly significant correlation was found between BCL-2 expression and tumour grade, with all Grade II and Grade III tumours showing positivity.MIB-1 (Ki-67) Index: MIB-1 positivity (>4\%) was observed in 9 cases (18%). A strong statistically significant correlation existed between MIB-1 expression and tumour grade, with higher values in Grade II and Grade III tumours. Marker Association: A significant association was noted between MIB-1 and BCL-2 expression, as BCL-2-positive cases showed higher MIB-1 positivity. All four cases (8%) with radiation-induced atypia demonstrated high BCL-2 and MIB-1 expression. **Conclusion:** This study demonstrates that most meningiomas are Grade I with a strong female predominance and intracranial localization. MIB-1 (Ki-67) index and BCL-2 expression both showed a significant association with higher tumour grade, indicating their usefulness as markers of increased proliferative activity and aggressive behaviour. While neither marker correlated with age, gender, or recurrence, their combined positivity was more frequent in higher-grade tumours. Thus, MIB-1 and BCL-2 immunoreactivity can serve as valuable adjuncts to routine histopathology for better assessment of tumour grade and biological behaviour in meningiomas.

KEYWORDS : Meningioma; Histopathology; Immunohistochemistry; MIB-1; BCL-2; Tumour Grade; Proliferation Index; Tumour Biomarkers.

INTRODUCTION

Meningiomas are the most common primary intracranial tumours, arising from arachnoid cap cells of the meninges[1,2,3]. Although predominantly benign, their clinical behaviour varies widely, ranging from slow-growing lesions to aggressive, recurrent, and higher-grade tumours[4,5]. The current WHO classification emphasizes histopathological features for grading; however, morphology alone may not fully predict prognosis or biological aggressiveness[6].

Immunohistochemical markers such as MIB-1 (Ki-67), a proliferation index, and BCL-2, an anti-apoptotic protein, have emerged as important adjuncts in assessing tumour behaviour. Elevated MIB-1 labelling indices are associated with increased mitotic activity, higher tumour grade, and recurrence risk[7,8]. Similarly, BCL-2 overexpression has been linked to tumour growth and resistance to apoptosis, potentially contributing to progression in higher-grade meningiomas[4,5].

Given the variability in clinical outcomes, correlating histopathological features with MIB-1 and BCL-2 expression may provide deeper insights into tumour biology and support more accurate prognostication. This study evaluates the histopathological spectrum of meningiomas and assesses MIB-1 and BCL-2 immunoreactivity to understand their significance in tumour grading and behaviour.

MATERIALS AND METHODS

Study Design and Setting

Cross-sectional observational study conducted in the Department of Pathology, Osmania General Hospital, Hyderabad, over a period of two years (January 2023 to December 2024). All surgically resected and histopathologically diagnosed meningioma specimens during this period were evaluated.

Study Population

The study population consisted of 50 patients diagnosed with meningioma based on histopathological examination. The population included:

- All age groups (children, adults, elderly)
- Both genders
- Patients with primary as well as recurrent tumours
- Patients with intracranial and intraspinal meningiomas

Sample Size and Selection Criteria

Inclusion Criteria

- Surgically excised meningioma specimens.
- Adequate formalin-fixed, paraffin-embedded tissue blocks.
- Both genders included.
- All WHO grades (I, II, III).
- Complete clinical and radiological data available.

Exclusion Criteria

- Cases without complete clinical or radiological information.

Data Collection

Data were retrieved from patient medical files, including:

- Age and gender
- Clinical presentation
- MRI findings and tumour location
- History of recurrence or radiation
- Surgical procedure performed

Gross Examination

All specimens were received in 10% neutral buffered formalin. Gross morphological features were documented:

- Tumour size and shape
- Surface characteristics
- Cut-surface texture
- Presence of necrosis, hemorrhage, or calcification
- Number of tissue bits sampled

Representative sections were processed for microscopic examination.

Histopathological Evaluation

H&E-stained sections were assessed for:

- Tumour subtype based on WHO 2021 classification
- Architectural pattern (whorls, syncytial pattern, psammoma bodies, fibroblastic areas)
- Features of atypia (mitotic activity, necrosis, sheeting, hypercellularity)
- Brain invasion
- Classification into Grade I, II, or III

Immunohistochemistry (IHC)

Antibodies Used

- MIB-1 (Ki-67): proliferation marker
- BCL-2: anti-apoptotic marker

IHC Procedure

- FFPE sections (3–4 μm) were mounted on coated slides.
- Deparaffinization and rehydration were followed by antigen retrieval.
- Endogenous peroxidase activity was blocked.
- Slides were incubated with primary antibodies and later with a secondary detection system.
- Visualization was achieved using DAB chromogen, followed by haematoxylin counterstain.

Scoring Criteria

- MIB-1 Labelling Index:
  - Counted in the most proliferative hot-spot areas.
  - Expressed as a percentage of positive tumour nuclei among 1000 cells.
- BCL-2 Expression:
  - Evaluated based on cytoplasmic staining intensity.
  - Graded according to percentage of positive tumour cells.

Statistical Analysis

- Data were compiled using Microsoft Excel and analysed with standard statistical software.
- The Chi-square test was applied to study associations between:
  - Tumour grade and MIB-1 expression
  - Tumour grade and BCL-2 expression
  - MIB-1 and BCL-2 correlation
- A p-value < 0.05 was considered statistically significant.

RESULTS

Demographics

- Mean age: 53.28 ± 10.11 years
- Age distribution: Majority between 30–59 years (39 cases, 78%)
- Gender: Males 34%, females 66%

Table 1: Age Distribution Pattern in Meningiomas

Age	No. of Cases	Percentage
10-19	1	2%
30-39	13	26%
40-49	13	26%
50-59	13	26%
60-69	5	10%
70-79	5	10%
Grand Total	50	100%

Table 2: Gender Distribution Pattern in Meningiomas

Gender	No. of Cases	Percentage
Male	17	34%
Female	33	66%
Grand Total	50	100%

Tumour Location

- Intracranial meningiomas: 47 cases (94%)
- Spinal meningiomas: 3 cases (6%)
- Most common sites: frontal region (18%) and CP angle (18%), followed by basifrontal and parietal regions (10% each).

Table 3: Distribution of Cases According to Location

Location	No. of Cases	Percentage
Intracranial	47	94%
Intraspinal	3	6%
Total	50	100%

Histopathological Findings

- WHO Grade I: 41 cases (82%)
- WHO Grade II: 2 cases (4%)
- WHO Grade III: 3 cases (6%)
- Radiation-induced atypia: 4 cases (8%)
- Common subtype: meningothelial (54%), followed by transitional (12%), angiomatous (8%), fibroblastic (6%), and psammomatous (2%).

Table 4: Distribution of Cases According to Grade

Grade	Count of Cases	Percentage
1	41	82%
Angiomatous	4	8%
Fibroblastic	3	6%
Meningothelilal	27	54%
Psammomatous	1	2%
Transitional	6	12%
2	2	4%
Atypical	2	4%
3	3	6%
Anaplastic	3	6%
Meningioma with radiation induced atypia	3	6%
Angiomatous meningioma with radiation induced atypia	1	2%
Grand total	50	100%

Recurrence

- 3 cases (6%) were recurrent; all were WHO Grade I.

Immunohistochemistry

BCL-2 Expression

- Positive in 12 cases
- Showed significant association with higher tumour grade ($p = 0.00035$)
- No significant correlation with age, sex, location, or recurrence.

Table 5: Correlation of BCL-2 with Respect to Histological Grades

Histological Grade	BCL-2 Negative	BCL-2 Positive
Grade 1	34	7
Grade 2	0	2
Grade 3	0	3
Total	34	12

It denotes extremely high statistically significance.

BCL-2 expression profiles differ significantly among tumour grades.

The high-grade tumours (grade 3) show complete BCL-2 positivity, while the low-grade tumours (grade 1) are mostly BCL-2 negative.

This suggests BCL-2 expression may be upregulated with tumour grade.

Caution is needed with the small number of cases for grades 2-3, the strong positivity of BCL-2 identifies it as a potential biomarker for tumour aggressiveness.

MIB-1 (Ki-67) Labelling Index

- High index (>4%) in 9 cases (18%)
- Strong correlation with tumour grade ($p = 1.29 \times 10^{-7}$)
- Significant association with tumour location ($p \approx 0.0098$)
- Positive correlation with BCL-2 ($p = 0.023$)

Radiation-Induced Atypia

- Four cases (8%) showed radiation-related atypical features.
- All demonstrated high MIB-1 and positive BCL-2 expression.

Table 6: Correlation of MIB-1 with Respect to Histological Grades

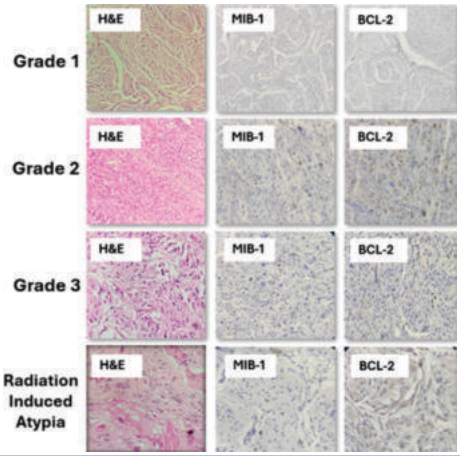
Grade	Negative	Positive
1	41	
2		2
3		3
Angiomatous meningioma with radiation induced atypia		1
Meningioma with radiation induced atypia		3
Grand Total	41	9

- P- value us 1.29×10^{-7}. There is an association between MIB-1 positivity and histological grade is highly statistically significant.

Correlation: BCL-2 expression was significantly associated with histological grade, being positive in all high-grade (Grade 3) tumours, but had no significant relation with age, gender, location, or recurrence. MIB-1 expression correlated strongly with tumour grade and specific locations (posterior fossa, sphenoid wing, and radiation-induced atypia), while showing no significant association with age, gender, or recurrence. Additionally, BCL-2 positivity was linked to higher MIB-1 indices, indicating increased proliferative activity.

DISCUSSION

Meningiomas are mostly benign CNS tumours arising from arachnoid cap cells[1]. In this study of 50 cases, WHO Grade I tumours (82%) predominated, with meningothelial subtype (54%) being most common. Grade II (atypical) and Grade III (anaplastic) tumours were less frequent.



Immunohistochemical analysis revealed that BCL-2 expression correlated strongly with tumour grade, being positive in all high-grade meningiomas, a finding supported by studies showing increased anti-apoptotic signalling in aggressive variants[2,3]. while MIB-1 (Ki-67) expression showed a highly significant association with grade and selected locations, indicating increased proliferative activity in aggressive tumours and radiation-induced atypia. Neither marker showed significant correlation with age, gender, tumour recurrence, or most anatomical locations, suggesting their primary relevance lies in assessing tumour aggressiveness rather than demographic or clinical variables.

In the fifth edition of the WHO Classification of Tumours of the Central Nervous System (WHO CNS edition 5)[9], meningiomas are recognized as a single tumour entity, encompassing a wide morphological spectrum represented by 15 distinct subtypes. It is emphasized that the criteria for atypical (Grade 2) and anaplastic (Grade 3) meningiomas should be uniformly applied, irrespective of the underlying histological subtype[10].

Notably, chordoid and clear cell meningiomas, due to their increased propensity for recurrence compared to conventional Grade 1 tumours, are classified as Grade 269. Nevertheless, validation through larger and prospective studies is necessary to reinforce these assignments and to identify additional prognostic biomarkers.

Historically, the presence of rhabdoid or papillary morphology was sufficient to classify a meningioma as Grade 370. However, emerging evidence suggests that grading should not be based solely on the presence of rhabdoid cytology or papillary architecture; rather, it should incorporate additional indicators of aggressive behavior[10].

Molecular advances have further refined the classification and prognostication of meningiomas. Specific genetic alterations, including SMARCE1 mutations (associated with the clear cell subtype), BAP1 mutations (linked to rhabdoid and papillary variants), and KLF4/TRAF7 mutations (characteristic of the secretory subtype), are increasingly recognized. Additional molecular events, such as TERT promoter mutations, homozygous deletion of CDKN2A/B (indicative of WHO Grade 3 assignment), loss of H3K27me3 nuclear expression (associated with poorer outcomes), and DNA methylation profiling, have emerged as critical tools in tumour characterization and prognostication[11].

Moreover, research into novel biomarkers for meningiomas continues to evolve. Newer candidates under investigation include somatostatin receptor 2A (SSTR2A), signal transducer and activator of transcription 6 (STAT6), SRY-box transcription factor 10 (SOX10), and various DNA methylation patterns, which may aid in distinguishing different subtypes and predicting clinical outcomes[12]. Despite these advances, epithelial membrane antigen (EMA) and progesterone receptor (PR) remain the most established immunohistochemical markers for meningioma diagnosis[10]. Continued research is essential to identify more specific and reliable biomarkers that can further enhance the diagnosis, grading, and management of meningiomas.

WHO CRITERIA FOR MENINGIOMA GRADING[10]

Benign meningioma (WHO GRADE I)

- Mitotic count of less than 4 per 10 HPF
- Histological variant other than clear-cell, chordoid, papillary, or rhabdoid
- Lacks criteria of atypical and anaplastic meningiomas

Atypical meningiomas (WHO GRADE II) (any of three criteria)

- Mitotic index= four mitoses/ten high power fields
- At least three of five parameters: Increased cellularity

High nuclear/cytoplasmic ratio (small cells) Prominent nucleoli Uninterrupted paternalism or sheet like growth Foci of spontaneous Necrosis (i.e, not induced by embolization or radiation)
- Brain invasion

Anaplastic (malignant) meningioma (WHO GRADE III) (EITHER OF TWO CRITERIA)
- Mitotic index = 20 mitoses /10hpf
- Anaplasia (sarcoma, carcinoma, or melanoma-like histology).

The most reliable histological correlate of recurrence risk is increased mitotic activity i.e., four or more mitoses per ten high power fields[10]. Nevertheless, in the absence of increased Mitotic activity, other histological features are associated with the likelihood of recurrence and therefore have grading implications[10].

Table 7: Comparison of the Mean of MIB-1 in Different Grades with Other Studies

Study	No. of Cases	Grade 1 mean Ki67LI	Grade 2 mean Ki67LI	Grade 3 mean Ki67LI
Present Study	50	0.76%	6.0%	12.33%
Pavelin et al13	62	1.5%	6.2%	10.2%
Karamitopoulou et al14	60	1.3 ± 3.2%	9.3 ± 6.9%	15.0±16.9%
Nuket et al15	246	2.61±5.68	8.61±11.77	11.79±14.0
Perry et al.16	581	1.6%	6.3%	14.7%
Roser et al.17	160	2.7%	8.7%	17.4%
Amatya et al18	146	1.5%	8.1%	19.5%
Abramovich et al19	90	1.0%	5.5%	12.%
Zorludemir et al.20	142	2.0%	8.2%	15.5%
Bruna et al.21	77	1.5%	7.5%	18%
Lüders etal.22	181	2.5%	8.2%	17.1%
Abry et al.23	119	1.2%	5.5%	13%

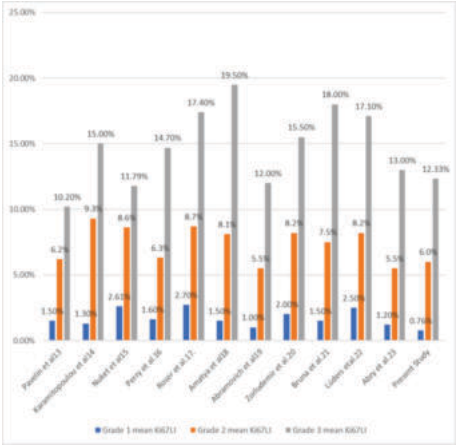


Chart 1: Comparison of the Mean of MIB-1 in Different Grades with Other Studies

In the present study, the mean Ki67 LI was 0.76% in grade 1 meningiomas, and those of grade 2 and grade 3 meningiomas were 6.0 % and 12.33% respectively.

In the present study the mean Ki67LI among Grade 1 meningiomas was correlating with the studies by Karamitopoulou et al[14], Abramovich et al[19]. Nuket et al[15] and Abry et al.[23]

Among Grade 2, the mean Ki67 LI was correlating with Pavelin et al[13], Nuket et al[15], Abramovich et al[66] Karamitopoulou et al[14], Perry et al.[16]and Abry et al.[23]

Among grade 3, the mean Ki67 LI was correlating with Nuket et al[15], Abramovich et al[19]and Abry et al.[23]

Grade 3 meningiomas were higher than the other Grade 1 & Grade 2 meningiomas, present study was in concordance with the other studies.

Amatya et al[18] in their study reported that generally, higher the MIB-1 index, higher is the grade of meningiomas and its tendency for recurrence which aligns with present study.

In our study, mean Ki67LI in recurrent tumours 1% whereas non recurrent tumour showed 2.64%

The problem with MIB-1 variability within the tumour grade in various studies, is because of tumour heterogenicity and sampling. The recorded MIB-1 should be determined in the area with the highest degree of positive staining, since it is particular area that determines the proliferative potential of the tumour. However, finding the area that has the highest proliferative capacity will depend on thorough sectioning and staining, which even when adhered to may not detect a minute focus of cells with a high proliferation rate.

A slide chosen for cell proliferation immunohistochemistry may or may not represent the most proliferative area of a given tumour. On the other hand, surgically removed tissue samples may not represent the most proliferative area of a given neoplasm. Moreover, there appears to be overlap in terms of labelling indices at the interface between tumour grades. All the issues should cause one to be cautious in the interpretation of labelling index. Despite all these limitations, cell proliferation markers are useful in selected circumstances.

Overall, the study supports the role of BCL-2 and MIB-1 as biomarkers for assessing tumour aggressiveness and proliferative potential. These findings align with prior studies, reinforcing the value of combining histopathology with immunohistochemistry for prognostication and planning long-term follow-up of meningioma patients.

CONCLUSION

Meningiomas are predominantly benign, intracranial tumours with a female predominance and occur mostly in the fourth to sixth decades of life. WHO Grade I tumours, especially the meningothelial subtype, are most common, while higher-grade (II and III) and radiation-induced atypical tumours show increased BCL-2 and MIB-1 expression, indicating higher proliferative activity.
- BCL-2 and MIB-1 expression correlates strongly with histological grade and tumour aggressiveness.
- MIB-1 may also relate to tumour location, particularly in posterior fossa and sphenoid wing regions.
- Long-term follow-up and larger studies are necessary to validate their prognostic significance and guide management.

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