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Original Article

Immnunohistochemichal Expression of IDH1, ATRX & P53 In Gliomas and Their Correlation with Clinicopathological Parameters

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ABSTRACT

Introduction: Central Nervous system tumor, one of the most lethal malignancies, is the seventeenth most prevalent cancer worldwide and accounts for 1 to 2 percent of all tumours. The incidence of central nervous system (CNS) cancers in India is between 5 and 10 per 1,000,000 people, with an upward trend. Gliomas are the most common tumours representing 26.5 % of all CNS tumours.

Aims: The aim of this study was to evaluate the immunohistochemical expression of IDH1, ATRX, and P53 in gliomas and to assess their correlation with clinicopathological parameters. The objectives included studying these markers in gliomas with clinicopathological correlation, evaluating the diagnostic accuracy of squash smear cytology, and correlating squash smear findings with histopathology in central nervous system lesions.

Materials & Methods: This was a combined retrospective and prospective study conducted over a period of 1 year, including 80 patients with histologically confirmed gliomas. Immunohistochemical expression of IDH1, ATRX, and P53 was assessed and correlated with clinicopathological parameters,

Result: Non-contributory ATRX expression was observed in 5.0% High Grade and 5.0% Low grade glioma cases. Loss of ATRX expression(ATRX mutation) was observed in higher proportion of High Grade glioma cases as compared to Low grade (87.5% vs. 52.5%), this difference was found to be significant statistically(p=0.001).

Conclusion: We concluded that immunohistochemical markers IDH1, ATRX, and P53 show significant diagnostic and prognostic value in gliomas and correlate well with clinicopathological parameters. Headache was the most common clinical presentation, and astrocytic tumours were the predominant histological subtype.

Keywords: Glioma; IDH1, ATRX; P53, Immunohistochemistry, Squash smear cytology, Astrocytoma

INTRODUCTION

Central Nervous system tumor, one of the most lethal malignancies, is the seventeenth most prevalent cancer worldwide and accounts for 1 to 2 percent of all tumours. The incidence of central nervous system (CNS) cancers in India is between 5 and 10 per 1,000,000 people, with an upward trend. Gliomas are the most common tumours representing 26.5 % of all CNS tumours. Gliomas arise from glial cells – the supporting cells, composed of 4 main type of cells : Astrocytes, Oligodendrocytes, Microglial cells and Ependymal cells. Diffuse gliomas are the most common primary brain tumor in adults, affecting about 20,000 people in the US each year [1]. Astrocytic tumors are the most common type of gliomas (70%) followed by oligodendroglial tumors (9%), which include classic oligodendrogliomas and mixed oligoastrocytomas [1].Glioblastoma makes for 56.1% of all gliomas and 15% of all intracranial neoplasms, making it the most prevalent tumour among gliomas [2]. With a median survival of 14 months and a 5-year survival rate of about 9.8%, it is highly aggressive tumour [3]. This type of tumour is particularly noteworthy because the incidence and fatality rates of brain

tumours have significantly increased in many developed countries. Primary glioblastomas are those that develop without lower grade precursors, astrocytomas that start as grade 2 or 3 and progress to secondary glioblastomas, or oligodendrogliomas that have the potential to develop into anaplastic oligodendrogliomas. With the exception of pilocytic astrocytomas, the prognosis of glioma patients is still poor. Less than 3% of glioblastoma patients are still alive at 5 years after diagnosis, higher age being the most significant predictor of poor outcome [4]. . The tumors can range from truly benign to overt malignant; however, the pathological differentiations from clinical and radiological parameters is often confusing.At times, intraoperative decision-making can be difficult due to the tumor location, pre-operative and anticipated neurological deficits. Incomplete resection of benign pathology can deny patient with the chance for cure. Squash cytology (SC) is a method of quick evaluation of cytomorphologic features prepared from smear technique that could provide the preliminary diagnosis, separating the low grade tumors from the high grade ones as well as differentiating non-neoplastic from neoplastic lesions. The aim of this study was to evaluate the immunohistochemical expression of IDH1, ATRX, and P53 in gliomas and to assess their correlation with clinicopathological parameters. The objectives included studying these markers in gliomas with clinicopathological correlation, evaluating the diagnostic accuracy of squash smear cytology, and correlating squash smear findings with histopathology in central nervous system lesions.

MATERIALS AND METHODS

Type of Study: Both retrospective and prospective study

Place of Study: Department of Pathology in collaboration with Department of Neurosurgery, King George's Medical University, Luck now.
Study Duration: 1 year
Sample Size: 80 patients

Inclusion Criteria:

- All histologically confirmed cases of gliomas diagnosed on biopsy or surgical specimens
- Patients of all age groups and both sexes
- Cases with available adequate formalin-fixed paraffin-embedded (FFPE) tissue blocks for immunohistochemical study
- Cases with complete clinical and radiological details
- Patients undergoing squash smear cytology and subsequent histopathological confirmation

Exclusion Criteria:

- Non-gliomatous central nervous system tumours
- Inadequate or poorly preserved tissue samples not suitable for immunohistochemistry
- Cases where complete clinical, radiological, or histopathological data were not available
- Recurrent tumours without primary diagnostic tissue available
- Patients who received prior chemotherapy or radiotherapy before biopsy (if applicable in study design)

Study Variables:

- Clinical variables: Age, sex, presenting symptoms (headache, vomiting, seizures, altered sensorium, etc.)
- Radiological variables: Tumour location, size, and preoperative grading (low-grade vs high-grade suspicion)
- Histopathological variables: Tumour type (astrocytic, oligodendroglial, mixed), WHO CNS 2021 classification, and tumour grade
- Immunohistochemical variables: Expression status of IDH1 (mutant/wild type), ATRX (retained/loss), and P53 (positive/negative or overexpression pattern)
- Correlative variables: Relationship of IHC markers with histopathological grade, tumour lineage, and clinical-radiological findings
- Cytological variable: Correlation of squash smear cytology with final histopathological diagnosis

Statistical Analysis:
Data were entered into Excel and subsequently analyzed using SPSS and GraphPad Prism. Continuous variables were summarized as means with standard deviations, while categorical variables were presented as counts and percentages. Comparisons between independent groups were performed using two-sample t-tests, and paired t-tests were applied for correlated (paired) data. Categorical data were compared using chi-square tests, with Fisher's exact test applied when expected cell counts were small. A p-value of ≤ 0.05 was considered statistically significant.

RESULT

Table 1 : Distribution of glioma according to Squash cytology and HPE correlation

SN	Correlation of HPE & Squash cytology	Frequency	Percentage
1	No	3	26.3

2	Yes	77	73.8

Table 2 : Diagnostic Accuracy of Squash as compared to Histopathology (n=79)

Squash Cytology	Histopathology High	Histopathology Low	Total
High	38	1	39
Low	1	39	40
Total	39	40	79

1 excluded

Parameter	Value (%)
Sensitivity	97.4
Specificity	97.5
PPV	97.4
NPV	97.5
Diagnostic accuracy	97.5

= 0.949 ; p<0.001

Table 3 : Association of ATRX expression with histopathological grade of tumor.

SN	ATRX Status	HGG (No, %)	LGG (No, %)	Total
1	Loss (Mutation)	56, 87.5	21, 52.5	77
2	Non-Contributory	4, 5.0	2, 5.0	6
3	Present (Retained)	20, 7.5	17, 42.5	37
$\chi2$=13.300; p=0.001				

Table 4 : Association of IDH1 expression with Histopathological Grade of Tumor

SN	IDH1 Status	HGG (No, %)	LGG (No, %)	Total (N=80)
1	Negative / Wild type	23, 45.0	5, 12.5	28
2	Non-Contributory	3, 2.5	2, 5.0	5
3	Positive / Mutant	54, 52.5	33, 82.5	87
$\chi2$=10.348; p=0.006				

Table 5 : Association of Histopathological Lineage and expression of different markers

	P53 Expression	Astrocytic (No)	Astrocytic (%)	Oligodend. (No)	Oligodend. (%)
1	Negative	15	21.4	7	87.5
	Non-contributory	0	0	0	0
	Positive	55	78.6	1	12.5
$\chi2$ = 55.490; p<0.001					
	ATRX Expression				
2	Loss	55	78.6	0	0
	Non-contributory	3	4.3	0	0
	Present	12	17.1	8	100
$\chi2$ =35.249; p<0.001					
	IDH1 Expression				
3	Negative	20	28.6	2	25
	Non-contributory	2	2.9	1	12.5
	Positive	48	68.6	5	62.5
$\chi2$ =2.343; p=0.676					

Figure 1: Distribution of glioma according to Squash cytology and HPE correlation

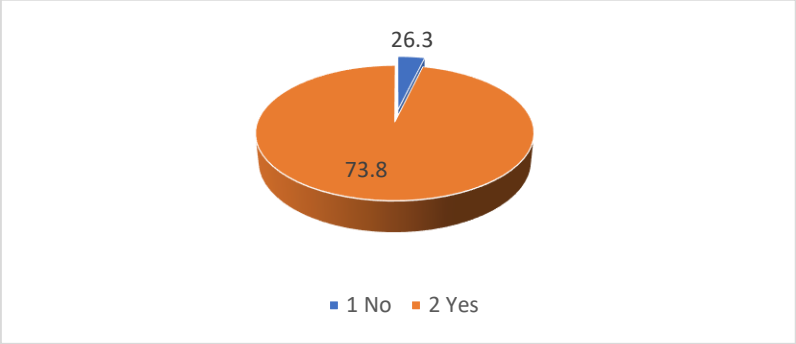
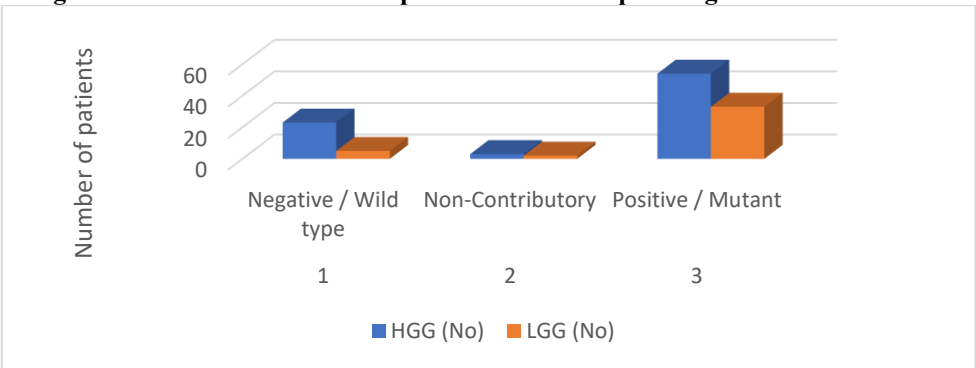


Figure 2: Association of IDH1 expression with Histopathological Grade of Tumor



Out of 80 cases, correlation of histopathological & Squash smear findings were observed for 77 (73.8%) cases. Squash smear finding of 1 case was inconclusive. Out of 79 cases agreement of Squash smear findings and Histopathological findings was observed for 77 (97.5%). Level of agreement was almost perfect. Diagnostic accuracy of Squash smear was found to be 97.5%, its sensitivity, specificity, PPV and NPV were 97.4%, 97.5%, 97.4% & 97.5% respectively. Squash cytology correlated with HPE in 77 cases.

Non-contributory ATRX expression was observed in 5.0% High Grade and 5.0% Low grade glioma cases. Loss of ATRX expression(ATRX mutation) was observed in higher proportion of High Grade glioma cases as compared to Low grade (87.5% vs. 52.5%), this difference was found to be significant statistically(p=0.001).

Positive IDH1 expression ie;IDH1 mutation was observed in significantly higher proportion of Low Grade glioma cases as compared to High Grade glioma (82.5% vs. 52.5%) and this was found to be statistically significant.

Majority of Oligodendrioglial glioma cases had negative p53 expression while majority of Astrocytic glioma cases had positive p53 expression. This difference was found to be significant statistically. ATRX expression was present in all the Oligodendrioglial and only 17.1% Astrocytic glioma cases. Majority of Astrocytic glioma cases had negative ATRX expression ie;loss of ATRX expression (ATRX muatation) in Astrocytic tumors. ATRX expression was found to be significantly associated with histopathological lineage. IDH1 expression did not show any significant association with histopathological lineage. P53 expression did not show any significant association with age, gender and presenting complaints. In cases with glioma at frontal site Negative p53 expression was found in significantly higher proportion (40.9% vs. 15.8%). ATRX expression did not show any significant association with Age, gender, site, and presenting complaints. IDH1 expression did not show any significant association with Age, site, and presenting complaints. Among males negative IDH1 expression was more prevalent (82.6% vs. 59.3%).

DISCUSSION

In the present study, squash smear cytology showed high concordance with histopathological diagnosis, with agreement observed in 77 out of 80 cases (97.5%). One case was inconclusive on squash smear. Among 79 evaluable cases, diagnostic accuracy was 97.5%, with sensitivity 97.4%, specificity 97.5%, PPV 97.4%, and NPV 97.5%, indicating almost perfect agreement. Similar high diagnostic accuracy was reported by Patil SS et al.[5] who emphasized squash cytology as a reliable intraoperative diagnostic tool in CNS tumors.

Loss of ATRX expression (ATRX mutation) was significantly more frequent in high-grade gliomas compared to low-grade gliomas (87.5% vs. 52.5%, p=0.001). This is consistent with findings of Nandakumar P et al [6] who demonstrated that ATRX loss is strongly associated with astrocytic lineage and higher-grade gliomas.

IDH1 mutation was significantly more common in low-grade gliomas than high-grade gliomas (82.5% vs. 52.5%). Similar findings were reported by Du N et al. [7] who identified IDH1 mutation as a key marker of lower-grade gliomas with better prognosis. However, no significant association with histopathological lineage was observed in the present study.

P53 expression was predominantly positive in astrocytic tumors and negative in oligodendroglial tumors, showing significant association with histological subtype. This is similar to findings of Noor H et al [8], who reported TP53 mutations mainly in astrocytic gliomas. No significant association with age, gender, or clinical presentation was observed .

ATRX expression was retained in all oligodendroglial tumors and lost in most astrocytic tumors, showing strong association with tumor lineage. This finding is supported by Wiestler B et al. [9] who described ATRX loss as a hallmark of astrocytic differentiation.

IDH1 expression did not show significant association with age, site, or presenting complaints; however, male patients showed higher frequency of negative IDH1 expression, which is consistent with observations of Hartmann C et al. [10] .

CONCLUSION

Squash smear cytology demonstrated a strong concordance with histopathological diagnosis, indicating that it is a reliable and rapid intraoperative diagnostic tool for central nervous system lesions. The level of agreement between the two modalities reflects its high diagnostic reliability and usefulness in routine neurosurgical practice, particularly for intraoperative decision-making.Among the molecular markers evaluated, ATRX loss was predominantly associated with high-grade gliomas and astrocytic lineage, suggesting its value in identifying more aggressive tumor biology and supporting astrocytic differentiation. In contrast, IDH1 expression was more commonly associated with low-grade gliomas, highlighting its role as a favorable prognostic marker and its utility in glioma classification. However, its association with histopathological lineage and other clinical parameters was not consistently significant, indicating variability in expression patterns.P53 expression showed a distinct association with tumor histology, being more frequently observed in astrocytic tumors compared to oligodendroglial tumors, thereby supporting its role in distinguishing glioma subtypes. However, its expression did not demonstrate a consistent relationship with clinical parameters such as age, gender, or presenting complaints.Overall, ATRX, IDH1, and p53 collectively contribute to improved histopathological classification of gliomas and enhance diagnostic accuracy when used alongside conventional morphology and squash cytology. These markers provide valuable insights into tumor lineage and biological behavior, thereby aiding in more precise diagnosis and better-informed clinical management of glioma patients.

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