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Role Of Immunohistochemistry In The Differential Diagnosis Of High Grade Gliomas And Metastatic Carcinomas

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Abstract

Background: Gliomas are tumours which originate in the glial cells of the brain or the spine. Differentiating primary central nervous system (CNS) gliomas from metastatic tumors using immunohistochemistry (IHC) is crucial in neuropathology

Aims/Purpose: The role of immunohistochemistry in the differential diagnosis of High grade Gliomas and metastatic carcinomas.

Method: Relevant clinical & radiological data was taken. Immunohistochemistry was done after H & E microscopy, according to the diagnostic need & integrated diagnosis was given.

Result: This study was carried out in the Department of Pathology at Mahatma Gandhi Medical College and Hospital, Jaipur, on total 45 cases of High grade Glioma and CNS metastasis. Glioblastoma CNS WHO Grade 4, Astrocytoma CNS WHO Grade 4, Oligodendroglioma CNS WHO Grade 3 and Metastatic carcinomas show male predominance with 90%, 66.66%, 69.2% and 84.61% respectively. Age group 41-50 years has the highest representation (31.11%) of all cases, followed by 61-70 years (26.66%) and 51-60 years. In glial tumors, GFAP expression demonstrated high statistical significance, exhibiting both 100% sensitivity and 100% specificity when compared to metastatic tumors. Pan-CK showed statistically significant expression in metastatic tumors, with a sensitivity of 100% and a specificity of 76.9%. Pan CK shows poor sensitivity for detection of Glial tumour – 9.3%.

Conclusion: The findings in the present study suggests that IHC serves as a reliable and effective technique for differentiating high-grade gliomas from metastatic tumors of CNS. The combined use of markers such as GFAP and PanCK has shown considerable value in differentiation.

Keywords: IHC, GFAP, PanCK, Glioma

Introduction

Tumors of the central nervous system comprise 1–2% of all neoplastic disorders.[1]

Gliomas are tumours of neuroepithelial tissues which originate in the glial cells of the brain or the spine.[1] Gliomas are typically categorized into three major types— astrocytoma, ependymoma, and oligodendroglioma based on the phenotypic characteristics of the cells from which they arise.

1. *Astrocytoma*: These arise from astrocytes and may present as well-demarcated lesions, maintaining distinct boundaries with surrounding brain tissue, or as infiltrative masses, typically associated with higher-grade tumors. While low-grade

astrocytoma are more frequently seen in pediatric patients, high-grade forms are predominantly observed in adults.

2. *Oligodendroglioma***:** These develop from oligodendrocytes and generally exhibit less infiltrative behaviour compared to astrocytoma. They are most frequently diagnosed in individuals during middle adulthood.
3. *Ependymoma:* These tumors originate from ependymal cells that line the ventricles of the brain and the central canal of the spinal cord. These tumors are more frequently observed in pediatric populations.

Gliomas constitute around 30% of all brain and central nervous system tumors and make up nearly 80% of all primary malignant brain neoplasms.[2]

The central nervous system is a frequent site for metastatic spread, with brain metastases occurring in approximately 10% to 50% of individuals with systemic cancers over the course of their illness.[3] Clinically, most diagnosed cases of CNS metastases originate from identifiable primary tumors; however, approximately 5–10% arise from unknown primary sites.[4]

Central nervous system metastases most commonly arise from primary cancers such as [5]:

•Lung carcinoma (18–60%)
•Breast carcinoma (5–21%)
•Melanoma (4–16%)
•Genitourinary tract malignancies (3–10%)
• Gastrointestinal cancers (5–12%)

Central nervous system metastasis occurs primarily when genetically unstable tumor cells acquire the ability to survive and proliferate within the distinct microenvironment of CNS tissue, which differs significantly from that of the primary tumor site.[6] Following detachment from the primary lesion, metastatic cells undergo genomic alterations, adopting new phenotypic traits while eliminating characteristics that are disadvantageous to survival in the new environment.[7] This adaptation is especially important in the development of CNS metastases, as tumor cells must acquire traits that enable them to breach the blood–brain barrier and successfully migrate across it.[8,9]

Poorly differentiated metastatic tumors within the CNS can be challenging to differentiate histologically from high-grade gliomas.[5] Histologically, high-grade gliomas exhibit features such as nuclear atypia, elevated mitotic activity, microvascular proliferation with glomeruloid patterns, and areas of necrosis—findings that are also commonly observed in poorly differentiated metastatic carcinomas.

The technique of immunohistochemistry (IHC) was first introduced by Coons *et al.*, in 1941. They developed an immunofluorescence method to identify specific antigens within frozen tissue sections. Despite its early development, the technique gained widespread use in surgical pathology during the 1990s. Immunohistochemistry combines principles of immunology and histology, relying on the specific interaction between antigens and antibodies to detect and localize target antigens within tissues or cells.

Effective use of immunohistochemistry requires understanding both the tissue's capacity to express a particular antigen and its precise intracellular localization.

Differentiating primary central nervous system (CNS) gliomas from metastatic tumors using immunohistochemistry (IHC) is crucial in neuropathology. Here's a description of key IHC markers that help distinguish CNS gliomas from metastatic carcinomas:

1. *Glial Fibrillary acidic protein (GFAP):* This is a monomeric intermediate filament protein expressed in mature astrocytes and specific other glial cells, but it is not absent in tissues outside the central nervous system. Elevated GFAP expression, indicative of astrocyte activation, is commonly regarded as a marker of gliosis or as a sign of gradually progressing neural injury. GFAP antibody shows positive immunoreactivity in tumor cells originating from various glial neoplasms, including astrocytoma, anaplastic astrocytoma, glioblastoma, mixed gliomas, and ependymomas. Roy and Sarkar were the first to isolate glial fibrillary acidic protein (GFAP) from chronic plaques associated with multiple sclerosis. Its molecular weight falls within the range of 40 to 50 kilodaltons (kDa). [10]
2. *Cytokeratins (CK):* Cytokeratins (CK) are intermediate filament proteins present in all forms of epithelial cells, making them reliable markers for identifying epithelial cell origin. They are categorized into 20 distinct subtypes, each

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assigned a specific number from 1 to 20, and their expression patterns are often specific to particular organs and tissue types. The specific cytokeratin subtypes expressed by epithelial cells vary not only with the epithelial type but also according to the cells' developmental stage and degree of terminal differentiation. An initial screening typically involves the use of 'pancytokeratin,' a mixture of cytokeratins found in the majority of epithelial tissues, commonly detected using the AE1/AE3 antibody cocktail. After establishing the epithelial nature of a tumor, specific cytokeratins like CK7 and CK20 are employed to further classify and characterize the epithelial neoplasm.[11]

The aim of this study is to evaluate the role of immunohistochemistry in differential diagnosis of High grade glioma and metastatic carcinomas.

Materials And Methods

Relevant clinical and radiological data was taken. All Neuropathological specimens of High grade Glioma and CNS metastasis were fixed in 10% neutral buffered formalin and were processed as per the standard guidelines. Immunohistochemistry was done after the H & E microscopy, according to the diagnostic need of the particular case and the integrated diagnosis was given.

Results

Male constitutes over 77.78% (35 cases) of all and Female representation is slightly lower at 22.22% (10 cases).This suggests a strong male predominance in our study. Among all 45 cases, Glioblastoma CNS WHO Grade 4, Astrocytoma CNS WHO Grade 4, Oligodendroglioma CNS WHO Grade 3 and Metastatic carcinomas show male predominance with 90%, 66.66%, 69.2% and 84.61% respectively. Among 32 cases of High grade glial tumors 24 (75%) were male, and 8 (25%) were female in a ratio of 3:1. In Glioblastoma CNS WHO Grade 4, males constitute 90% of the cases, while females make up 10% in a ratio 0f 9:1. In Astrocytoma CNS WHO Grade 4, male constitute 66.66% and female constitute 33.33% in a ratio of 2:1. In Oligodendroglioma CNS WHO Grade 3, males constitute 69.2% while females constitute 30.7% in a ratio of 7:3

Metastatic carcinomas also show male predominance, with males making up 84.61% of the case and females 15.38% in a ratio of 5.5:1

High grade glioma and metastatic tumor both show male predominance. Age group 41-50 years has the highest representation (31.11%) of all cases, followed by 61-70 years (26.66%) and 51-60 years (20%).

In Glioblastoma CNS WHO Grade 4, most of the cases are in age group 41-50 years and 61-70 years with equal incidence (30%). Most common age group in Astrocytoma CNS WHO Grade 4 is 41-50 years (55.55%), in Oligodendroglioma CNS WHO Grade 3 is 51-60 years (30.76%) and in Metastatic carcinomas is 61-70 years (38.46%). among all 45 cases, Oligodendroglioma CNS WHO Grade 3 are 28.88%(13 cases), Glioblastoma CNS WHO Grade 4 are 22.22% (10 cases), Astrocytoma CNS WHO Grade 4 are 20% (9 cases) and metastatic carcinomas are 28.88% (13 cases).

This shows that Oligodendroglioma CNS WHO Grade 3 accounts for maximum number of cases reported in our study which is closely followed by Glioblastoma CNS WHO Grade 4 amongst High Grade Gliomas and proportion of cases of Oligodendroglioma CNS WHO Grade 3 is equivalent to metastatic carcinomas.

In the current study, glial tumors exhibited widespread reactivity for GFAP, with all cases (100%) demonstrating positive expression. Metastatic tumors were negative for GFAP and reactive for Pan CK. PanCK expression was generally absent or minimal in glial tumors. GFAP expression in glial tumors showed statistically significant results, demonstrating both 100% sensitivity and 100% specificity when compared to metastatic tumors. Pan-CK expression in metastatic tumors was found to be statistically significant, exhibiting a sensitivity of 100% and a specificity of 76.9%. Pan CK shows poor sensitivity for detection of Glial tumour – 9.3%. Statistically there is highly significant difference in both tumors as per immunohistochemistry.

Discussion

The above study was conducted in Department of Pathology, Mahatma Gandhi Medical College and Hospital, Sitapura, Jaipur on 45 cases to study role of immunohistochemistry in the differential diagnosis of High grade glioma and metastatic carcinomas.

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In situations where morphology alone is not enou gh to differentiate between high grade gliomas and metastatic carcinomas, immuno histochemistry (IHC) is essential. IHC aids in differentiating between distinct tumou r kinds, directing treatment choices, and enhancing di agnostic precision by employing certain antibodies to detect protein expression patterns.

High grade gliomas and metastatic carcinomas exhibits sex specific differences not only in incidence but also in survival, treatment response and molecular characteristics. This may occur due to hormonal factors or biological differences. In our study, male preponderance was observed in both High grade glioma and metastatic carcinoma with 77.78% cases. Further among High grade glial tumors 4 (75%) were male, and 8 (25%) were female in a ratio of 3:1. Metastatic carcinomas also show male predominance, with males making up 84.61% of the case and females 15.38% in a ratio of 5.5:1. Our results correlates with the study of Panel Jiale Yin [12], Ruchika Verma et al[13] and Wang GM[14] with male predominance in incidence of above carcinomas. Difference in Hormonal receptor and metabolic activity was the explained reason behind this difference.

But there is no significant difference in distribution of high grade glioma and metastatic tumor according to gender. It means both are common in males. Our findings are similar with study of Panel Jiale Yin [12], Ruchika Verma [13] and Wang GM.[14]

Glioma incidence and survival are significantly influenced by age, which is a major determinant in the incidence and survival of all malignancies. The incidence of gliomas peaks between the ages of 45 and 65, and they are more prevalent in older persons. In our study, age group 41-50 years has the highest representation (31.11%) of all cases, followed by 61-70 years (26.66%) and 51-60 years. Mean age of High Grade Glioma and Metastatic carcinomas around 50.56 years with Standard deviation of 12.2 years. In Glioblastoma, classified as CNS WHO Grade 4, the highest incidence was observed equally among individuals aged 41–50 years and 61–70 years. Most common age group in Astrocytoma CNS WHO Grade 4 is 41-50 years, in Oligodendroglioma CNS WHO Grade 3 is 51-60 years and in Metastatic carcinomas is 61-70 years. There is no statistical difference in both tumors according to age group. Our results are similar to the study of Lin Z [15] and Brennan CW[16], who noted that advancing age progressively diminishes natural immunosurveillance and compromises the effectiveness of immunotherapy against malignant gliomas. With increasing age, immunosuppressive activity within the brain intensifies, leading to reduced anti-glioma immune responses in older individuals. These results suggest that cellular immunity may contribute to the pathogenesis of brain and other CNS tumors in an age-dependent manner and highlight the importance of integrating emerging evidence on sex-based differences in immune suppression and tumor microenvironment interactions.

Our study shows that Oligodendroglioma CNS WHO Grade 3 accounts for maximum number of cases reported in our study amongst High Grade Glioma and proportion of cases is equivalent to number of metastatic tumour.

Glial tumors showed GFAP positivity in 100% cases while Metastatic tumors were negative for GFAP. Pan CK shows detection of glial tumours only in 9.3% cases while detects metastatic carcinoma in 100% cases.

Statistically there is highly significant difference in both tumors as per immunohistochemistry.

According to some studies [17,18], the presence of both pan-cytokeratin (pan-CK) and glial fibrillary acidic protein (GFAP) positivity in high-grade gliomas can be suggestive of a mixed glial and epithelial development in certain tumour cells. In particular, pan-CK is a marker for epithelial cells and GFAP is a diagnostic for astrocytic cells. Both markers' presence raises the possibility that the tumour contains aspects of both astrocytic and epithelial differentiation, which could point to a less differentiated and more aggressive tumour form.

Our results are similar to the study of Yang et al [21] and Prayson et al [22] who state that GFAP positivity was observed in all glioblastomas and that GFAP expression was absent in most metastatic tumours. According to this study, metastatic carcinomas, especially those from the lung, breast, and colon, were completely GFAP-negative, while 85% of GBMs were found to express GFAP. According to Prayson (2013) [21], the degree and intensity of GFAP staining in suspected glioma patients can frequently indicate the grade and

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prognosis of the tumour. GFAP positivity is a crucial characteristic of high-grade gliomas such as GBM, particularly when necrosis and pseudopalisading cells are present.

Numerous studies have correlated GFAP and CAM5.2 staining in glial and metastatic tumours, demonstrating that the combination of GFAP and CAM5.2 can be utilised to distinguish high-grade gliomas from CNS metastatic tumours. [23-27]

On the contrary, Shinoda et al. (2007) [28] pointed out that GFAP may not always be present in low-grade gliomas and certain variants like oligodendrogliomas, making its utility in these cases less reliable. Additionally, some studies suggest that GFAP can be used in conjunction with other markers to enhance the precision of diagnosis, particularly when the tumor presents with mixed histological features.

As far as PanCK is considered our results were in accordance to Prayson [20] and Luna et al [29] who studied that in metastatic tumours with epithelial origins, PanCK positive is virtually universal. For instance, PanCK positive is frequently seen in lung adenocarcinomas, which makes it a very accurate indicator of lung-to-brain metastases.

Further, Luna et al [29] explained PanCK's limitations despite its excellent sensitivity, PanCK has drawbacks when it comes to identifying epithelial metastases. Since some tumours, such melanomas and some sarcomas, do not express PanCK, this marker may miss them. Additionally, pancytokeratin may exhibit weak or focal positive in rare instances of gliomas with mixed histological characteristics or regions of epithelial development (such as gliosarcoma), which could make interpretation more difficult.

On the contrary our result contradicted to some studies. In, a research by Yang et al. (2011) [19], majority of melanoma and lymphoma displayed negative PanCK staining, suggesting that PanCK is not a reliable pan-metastatic marker. Furthermore, some sarcomas may have focal or poor PanCK expression, which could make diagnosis difficult. Further according to Kriho et al.[30], both malignant and normal astrocytes can test positive for GFAP and nonspecific PanCK, but not for the monoclonal antibody CAM5.2. This is because these tissues contain keratin polypeptides.

Hence the combination use of GFAP and PanCK has been investigated in numerous studies to improve diagnostic accuracy in differentiating high-grade gliomas from CNS metastases, given the advantages and disadvantages of each individual marker. By using both GFAP and PanCK, pathologists can rule out the likelihood of epithelial metastasis (using PanCK) and confirm the tumor's astrocytic lineage (using GFAP). This was explained by a study of Mandel et al [31] who demonstrated that the combination of GFAP and PanCK markers enhanced diagnostic sensitivity and specificity to more than 95%, with GFAP being present in gliomas and PanCK in CNS metastases. This dual approach facilitated a clear distinction in instances where tumor morphology was unclear, such as in cases suspected of gliosarcomas or metastatic tumors exhibiting epithelial characteristics. Additionally, Prayson (2013)[21] identified that a GFAP+/PanCK- pattern is a strong indicator of gliomas, whereas a GFAP-/PanCK+ pattern is highly suggestive of an epithelial metastatic tumor. This combination proves particularly valuable in situations where tumor morphology overlaps or the primary source of metastasis remains uncertain.

Conclusion

High-grade gliomas are frequently encountered in routine surgical neuropathology. Distinguishing them from metastatic tumor is critical, yet challenging, often due to factors such as necrotic tissue presence and limited biopsy sample specimen size resulting from stereotactic biopsy procedures. In this study, no statistically significant differences were noted in the age and gender distribution of both tumors.

The findings in the present study suggests that IHC serves as a reliable and effective technique for diagnosing CNS tumors and in differentiating high-grade gliomas from metastatic tumors of CNS. The use of markers such as GFAP and PanCK has shown considerable value in differentiation.

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Table:1Gender wise distribution of histologic subtypes of High Grade Glioma and metastatic carcinomas

	Glioblastoma Garde 4		Astrocytoma Grade 4		Oligodendroglioma Grade 3		Metastatic carcinomas	
	NO.	%age	NO	%age	No.	%age	No..	%age
Male	9	90%	6	66.66%	9	69.2%	11	84.61%
Female	1	10%	3	33.33%	4	30.7%	2	15.38%
Total	10	100%	9	100%	13	100%	13	100%

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Total: 45 cases								

CHI SQUARE- 2.4082

P VALUE- 0.49

Table 2: Age wise distribution of various histologic subtypes of High Grade gliomas and metastasis.

Age Group	Glioblastoma CNS WHO Garde 4		Astrocytoma CNS WHO Grade 4		Oligodendroglioma CNS WHO Grade 3		Metastatic carcinomas	
	NO.	%age	NO	%age	No.	%age	No..	%age
0-10 Years	0	0%	0	0%	0	0%	0	0%
11-20 Years	0	0%	0	0%	0	0%	0	0%
21-30 Years	1	10%	0	0%	0	0%	1	7.69%
31- 40 years	1	10%	3	33.33%	2	15.38%	1	7.69%
41-50 Years	3	30%	5	55.55%	3	23.07%	3	23.07%
51- 60 Years	2	20%	0	0%	4	30.76%	3	23.07%
61-70 Years	3	30%	1	11.11%	3	23.07%	5	38.46%
71- 80 Years	0	0%	0	0%	1	7.69%	0	0%
TOTAL	10	100%	9	100%	13	100%	13	100%

CHI SQUARE- 1.98

P VALUE- 0.53

Table 3: Frequency of various histologic subtype of High Grade Gliomas and Metastatic carcinomas

Tumour Type	Frequency (n)	Percentage (%)

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GLIOBLASTOMA-IDH WILD TYPE- CNS WHO GRADE 4	10	22.22%
ASTROCYTOMA-IDH MUTANT-CNS WHO GRADE 4	9	20%
OLIGODENDROGLIOMA-IDH MUTANT-CNS WHO GRADE 3	13	28.88%
METASTATIC CARCINOMA	13	28.88%
TOTAL	45	100%

Table 4: Correlation of GFAP And PAN CK staining in High Grade Gliomas and Metastatic Carcinomas.

TUMOUR TYPE	TOTAL CASES	GFAP POSITIVE		PAN-CK POSITIVE	
		NO.	(%)	NO.	(%)
GLIOBLASTOMA-IDH WILD TYPE- CNS WHO GRADE 4	10	10	100%	2	10%
ASTROCYTOMA-IDH MUTANT- CNS WHO GRADE 4	9	9	100%	0	0%
OLIGODENDROGLIOMA-IDH MUTANT-CNS WHO GRADE 3	13	13	100%	1	7.6%
METASTATIC CARCINOMA	13	0	0%	13	100%

Chi square- 30.82

P value <0.0001

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