ORIGINAL ARTICLE

Histopathological Study and Clinical Correlation of Glial Tumors at a Tertiary Care Hospital of Karachi

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ABSTRACT

Objective: To observe the spectrum of glial tumors in a resource-limited tertiary care setup of Karachi according to the modified WHO central nervous system tumor classification.

Study Design: A retrospective analysis.

Place and Duration of Study: The study was conducted at the Oncology Ward of Jinnah Postgraduate Medical Centre (JPMC), Karachi, Pakistan from August 2020 to January 2021.

Methods: The study was done to record data of patients diagnosed with glioma, which were registered during 2017 - 2019. Patients were classified according to recent WHO brain tumor classification. Data analysis as performed by SPSS version 26.0.

Results: A total of 115 glioma cases were included. The most common presenting age group was in the 4th decade of their life. Oligodendroglioma was the most common histological type 61 (53.5%). The most common presenting symptom was a headache in 46 (40%). The location of the tumor was temporoparietal lobe in 51/115 (44.3%). Immunohistochemical studies showed a significant association with histological subtypes (*p*-value: 0.002).

Conclusion: Oligodendroglioma was found to be the most common histological type. Immunohistochemical marker GFAP expression was positive for the majority of diagnosed cases, where 1p19q / codeletion was observed specifically in oligodendrogliomas.

Keywords: *Brain Tumor, Glioma, Glial Tumors, GFAP, immunohistochemistry.*

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Introduction

Gliomas are one the most frequently occurring tumors of the central nervous system. According to the Central Brain Tumor Registry of the United States CRBTUS, approximately 30% of brain tumors are Gliomas.[1] Normal glial tissue helps in providing structural support by myelination and making blood blood-brain barrier. Additionally, it helps in neuronal function.[2] GLOBOCAN, a project of the International Agency for Research on Cancer (IARC), estimated the number of newly diagnosed cases of Brain and CNS that was 256/100000 making 1.8% of the tumor burden. The mortality rate due to brain tumors was found to be 189/100000.[3] Glioblastoma is the most aggressive tumor type with an incidence rate of 3.19 per million in the United States. It was found to be more common in males than females and mostly involves the supra tentorial region, it has a median survival of 3 months in untreated cases.[4] Shaukat Khanum annual cancer registry 2021 showed Gliomas have a frequency of 3.3%, making them the ninth most prevalent form of cancer in Pakistan.[5]

Symptoms depend on the part of the brain involved

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and have reportedly presented with episodes of either headaches, nausea, or vomiting. In some cases, they may also present with seizures, loss of balance, gait difficulties, hearing alterations, or visual disturbances.[6,7] Involvement of optic chiasm and optic tract may present as visual field defects, vision loss, nystagmus, and retinal degeneration.[8]

The updated WHO classification of 2016 includes grading of glial tumors based on molecular alterations. This classification provides a significant prognostic and therapeutic approach. Isocitrate dehydrogenase (IDH) 1 & 2, ATRX gene mutation, 1p/19q co deletion, and TERT mutation, among others, are the key diagnostic genetic markers of gliomas. Previously, according to the World Health Organization (WHO) 2007, they were classified on histological grounds into Grade II (low grade), Grade III (anaplastic), and Grade IV (Glioblastoma). The modified classification, WHO 2016, and further additions do not grade glial tumors on the basis of morphology alone. All diffuse gliomas, whether they are astrocytic or oligodendroglia are classified currently by considering their growth pattern, clinical behavior as well as a mutation in the IDH gene. This differentiates tumors, in particular, astrocytoma (such as pilocytic astrocytoma, subependymal giant cell astrocytoma, and Pleomorphic Xanthoastrocytoma), that have more circumscribed growth, lack IDH gene modifications, or have BRAF mutation.[9,10] Advancement in classifications in terms of pathological point of view has also helped in better understanding of glial tumors. Providing sub-classifications of different major forms of gliomas and discussing their molecular origin provides a better opportunity to understand their pathogenesis.[11]

The modern-day diagnosis of glial tumors depends on the updated WHO classification. However, being in a resource-limited setup with major financial constraints and where molecular diagnostic options are not frequently available, only a limited number of markers and mutations can be identified. Thus, the current study was designed to observe the spectrum of glial tumors in a resource-limited tertiary care setup of Karachi, considering few available molecular alterations of the modified WHO central nervous system tumor classification.

Methods

The study was conducted in the Oncology Ward of Jinnah Postgraduate Medical Centre (JPMC), Karachi, Pakistan from August 2020 to January 2021, after obtaining ethical approval from the institutional review board of Jinnah Post Graduate Medical Centre (JPMC) Karachi, Pakistan vide letter no IRB no-44373 dated May 05, 2020. Data from patient records was collected from the record room of the Department of Oncology, JPMC. Medically diagnosed and registered glioma cases presented from 2017 to 2019 were included in the study. The rest of the brain tumor types were excluded. Patients under the age of 15, reports and documents that were not complete, and foreign nationals were excluded. Using a self-administered pro forma, data was gathered. The pro forma was created following a thorough literature review utilizing Google Scholar and PubMed. There were three parts to it. The first section included questions on demographics, family history, and location. Clinical characteristics upon presentation and the length of symptoms were covered in the second section. The third section consisted of biopsy findings including immune markers and CT reports findings. The IBM Statistical Package for the Social Sciences (SPSS), Version 25.0, was used to analyze the data. For numerical variables, the mean and standard deviations were calculated. Frequency and percentages were used to present categorical variables. Fisher's exact and chi-square was applied to calculate the statistical difference in morphological, immunohistochemical, and molecular profile distribution. A *p*-value of 0.05 or lower was regarded as significant.

Results

A total of 115 glioma cases were included. Males were 78 (67.8%) and females were 37 (32.1%). The age range was between 15 to 73 years, Mean=38.41, Standard deviation ±14.103. The most common presenting age group was in the 4th decade of their life. Oligodendroglioma was the most common histological type 61 (53.5%) followed by glioblastoma 25 (21.9%). Other morphological types included astrocytoma, diffuse glioma, paraganglioma, and brain stem glioma. The location of the tumor was the temporoparietal lobe in 51/115 (44.3%) followed by the frontal lobe 36/115 (31.3%).

Table 1 demonstrates the association between histological type and location of the tumor. The most common presenting symptom was a headache in 46 (40%) followed by unilateral weakness in 19 (16.5%) and fits in 11 (9.5%) cases, respectively Table 2 shows the frequency of the sign and symptoms cross-tabulated with histological subtypes which were found to be statistically non-significant i.e. p >0.05. A total of 43 (43.9%) of patients visited the doctor after 2 months for their presenting symptoms. Whereas the other 20(20.4%) and 25 (25.5%) presented within 2 months and 1 month, respectively. Only 10 (10%) patients visited the hospital within 2 weeks after the appearance of symptoms.

Table 1: Location of glioma associated with histological type

	Location of Tumor							
Histological type	**Frontal**	**Occipital**	**Temporoparietal**	**Infratentorial**	**Parietooccipital**	**Frontoparietal**	**Spinal cord**	**Total**
Oligodendroglioma	24	4	28	1	2	2	1	62
Glioblastoma	7	1	15	1	1	0	0	25
Astrocytoma	5	2	3	0	1	1	1	13
Paragon Glioma	0	0	0	2	0	0	0	2
Glioma	1	0	4	3	0	1	0	9
Brainstem Glioma	0	0	0	2	0	0	0	2
Diffuse glioma	0	1	1	0	0	0	0	2
	37	8	51	9	4	4	2	115

Table 2: Association of presenting complaint and histological subtype

Presenting complain	**Histological type**							**Total**
	Oligodendroglioma	**Glioblastoma**	**Astrocytoma**	**Paragon Glioma**	**Glioma**	**diffuse Glioma**	**Brainstem Glioma**	
Difficulty in speech	2	2	1	0	0	0	0	5
body pain	3	2	0	0	0	0	0	5
Swelling	0	0	1	0	0	0	0	1
headache	25	10	5	1	3	1	1	46
visual disturbance	0	0	1	1	1	0	0	3
Acute loss of consciousness	5	1	0	0	0	0	0	6
unilateral weakness	8	5	2	0	2	1	1	19
Fits	7	2	2	0	0	0	0	11
quadriplegia	1	0	0	1	0	0	0	2
Vomiting	3	2	0	0	2	0	0	5
dizziness	4	0	1	0	1	0	0	6
involuntary movements	3	1	0	0	0	0	0	4
	61	25	13	3	9	2	2	115

Midline shift was present in 23/115 (20%) patients, of which 11 (47.8%) patients suffered from temporoparietal tumors. However, the size of tumors did not show a significant association with midline shift (p-value= 0.518). GFAP expression was positive in 45 (55%) cases followed by GFAP and ki67 in 16 (19.5%). Also, in this study, immunohistochemical studies were also recorded to observe the expression of GFAP, Ki67, 1p/19q co deletion, and S100 which showed significant association with histological subtypes (p-value: 0.002) Table 3.

Table 3: Immunohistochemical profile and histological types of glial tumors

Immunohistochemistry	**Histological type**							
	Oligodendroglioma	**Glioblastoma**	**Astrocytoma**	**Paragon Glioma**	**Glioma**	**diffuse Glioma**	**Brainstem Glioma**	**Total**
Olig 2	0	0	0	0	0	1	0	1
GFAP positive	37	12	10	1	2	1	0	63
triple positive plus gene mutation	1	0	0	0	1	0	0	2
Ki67	1	0	0	0	1	0	0	2
1P	5	0	0	0	1	0	0	6
GFAP and Ki67 positive	6	11	3	0	2	0	1	23
19q deletion	1	0	0	0	0	0	0	1
GFAP and 1p/19q deletion	4	1	0	0	1	0	1	7
Triple Positive	3	1	0	0	0	0	0	4
S100	3	0	0	2	1	0	0	6
	61	25	13	3	9	2	2	115

Discussion

Glioma is one of the less common yet lethal types of brain tumors, a dearth of literature being documented from this region led us to report this malignancy from one of the most visited tertiary care hospitals of Karachi, Hence, a retrospective cohort was designed to observe the demographics, frequency, clinical presentation, morphological patterns, immunohistochemical profile and mutational spectrum of Gliomas.

A frequency of 2.2% of glioma was noted in the current analysis, among all the cases reported of different cancers. It is close to the annual cancer registry report 2018 of SKMCH&RC (3.3%).[5] Male to female ratio was 2.1:1 in comparison to a study from the University of Jordan which also reported a male majority (1.6:1). This is an interesting finding from the subcontinent region as the GLOBOCAN 2018 also revealed a considerable variation in gender distribution in the past decade.[3]

The present study showed that Oligodendroglioma was a predominant morphological type, and constituted almost half of the cases, followed by glioblastoma. On the contrary, another study from Pakistan reported astrocytoma as the most common morphological type followed by Oligodendroglioma.[10] Moreover, almost half of the gliomas were recorded in the temporoparietal region, followed by the frontal lobe. Similar statistics regarding the highest frequency of malignancy in the temporoparietal lobe have been reported by the CBTRUS statistical report of 2011-2015.[1]

The duration of presenting complaints was more than 2 months in almost half of the patients and about half of those cases were high-grade gliomas. Presenting complaint of headache in such cases of glioma can be of various types such as tension headache and classical brain tumor headache[11], similarly, our study reported headache as the most common complaint because of the mass effect produced by tumors larger than 3 cm in the longest dimension (p-value = 0.007).

Moreover, the location of the tumor showed a significant association with the presenting complaint in a study from Florida[6] and another case-control study[8], but any such correlation was not observed in our study (p-value = 0.146).

According to the new WHO classification, mutation types must be added to the morphological patterns of brain tumors. Main molecular markers in gliomas are IDH, 1p19q deletion, MGMT, TERT, ATRX, and p53.[9] In the current study, expression of GFAP, Ki67, 1p/19q co deletion, and S100 was noted to be in significant association with histological subtypes (p-value= 0.00).

Glial fibrillary acidic protein (GFAP) is a marker of increased proliferation in malignant cells and its levels are increased with the increase in histologic grade.[12] GFAP was positive in more than two-thirds of our cases, of which almost half were oligodendroglioma. A study in India also suggested that GFAP can be used for astroglia differentiation in difficult cases.[13] Ki 67 has also a significant role in glioma recurrence and in a study of relapse glioma, the expression of Ki67 along with p53 was evident.[14]

Co deletion of 1p/19q has shown an important association with treatment and survival rates. Studies have concluded a better prognostic rate in high-grade tumors that were positive for co-deletion[15,16] constituted 13% of cases in our study.

One important mutation in glioma is the Isocitrate dehydrogenases (IDH) 1 & 2 mutation, which is a key metabolic enzyme in reducing glutathione and peroxiredoxin.[17] Clinically IDH mutation status helps in diagnosing gliomas of moderate to high grade in early stages.[18] IDH 1&2 mutations have been reported to have a better prognostic effect in anaplastic astrocytoma and glioblastomas. In addition, it also resulted in better survival in operative cases when analyzed with preoperative inflammatory markers.[19,20] Due to low resources and financial constraints, IDH, MGMT, TERT, ATRX and p53 mutational profile of registered glioma patients could not be carried out in our setup.

Conclusion

Glioma represents a less common malignancy in the local population of Karachi. Oligodendroglioma was the most frequent histological type. Immunohistochemical marker GFAP expression was positive for most tumors, whereas 1p\١٩q codeletion was observed specifically in oligodendrogliomas.

Limitations

There were limited financial resources for carrying

out complete molecular profiles of the included cases. Despite that, available markers were used to assess and classify each case with less to no error.

Authors Contribution

JK: Data collection, data analysis, results and interpretation

IAB: Idea conception, study designing, data analysis, results and interpretation, manuscript writing and proof reading

NJ: Idea conception, Study designing, manuscript writing and proof reading

GH: Data collection, manuscript writing and proof reading

AZ: Data analysis, results and interpretation, Manuscript writing and proof reading

SMS: Data collection

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